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PROBLEMS OF  
NERVOUS ANATOMY





# PROBLEMS OF NERVOUS ANATOMY

BY

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## PREFACE

THE purpose of this book is to give an account of some of the fundamental problems concerning the anatomy, physiology, and function of the human nervous system. It is the outcome of three lectures delivered in England by invitation of the Universities of London and Oxford in November 1937, and a fourth lecture delivered before the Anatomische Gesellschaft at their annual meeting in Königsberg in September 1937. This fourth lecture was added because it deals with the general principles underlying details discussed in the three lectures delivered in England. It has been somewhat rearranged for the purpose of this publication and in order to avoid too much repetition.

There is naturally much personal research and conviction embodied in this book; however I have endeavoured to remain as objective as possible and to include other opinions concerning the problems under discussion. In the last chapter, in which the neurone theory is discussed, I have attempted to give an account of the difficulties which arise when this hypothesis is regarded by workers in the fields of anatomy and physiology as a fact rather than a theory. Students in the twentieth century tend to regard nature and organisms far more as a whole and less from the point of view of cellular independence within the organism than did their predecessors. It therefore becomes dangerous to base present-day research upon the neurone theory in its classical form enunciated fifty years ago. Research becomes sterile unless we attempt to take into account the advances made in science generally during the course of the last thirty years. The science of anatomy cannot advance unless research within this field follows current physiological thought.

Histology is interesting only when it gives a better insight into the function of the tissue or element under discussion. Theories based upon principles once commonly accepted but now obsolete are apt to lead to an uncompromising attitude which kills progress. The words of Claude Bernard may well be quoted here: 'Il faut chercher à briser les entraves des systèmes philosophiques et scientifiques, comme on briserait les chaînes d'un esclavage intellectuel.' This progressive outlook does not of course in any way detract from the historical value of such theories or from the genius of those who formulated them.

I wish to acknowledge with gratitude a grant from the University of London which makes this publication possible and also desire to express my appreciation of the kindness of the delegates of the Clarendon Press who agreed to publish this book at such a time as the present.

J. B.

UTRECHT

*November 1939*

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## CHAPTER I

### CHANGES IN THE SPINAL AND SYMPATHETIC INNERVATION OF THE SKIN DURING DEGENERATION AND REGENERATION

THE histological basis of the sympathetic and spinal innervation of the different parts of the body, including that of the nerve-endings, is surely a problem worthy of attention ; for, as I hope to show, not only does the body as a whole come under the influence of the nervous system, but even the most subtle functions of the skin, the connective tissue, and the glands of internal secretion, &c., are under the control of the sympathetic nervous system. Thus in disease, visceral and otherwise, the importance of the sympathetic nervous system can hardly be exaggerated. In the skin sympathetic nervous influence on fat cells, as well as on sebaceous glands and connective tissue, can be detected everywhere.

However, as we shall see, our knowledge concerning the anatomy of this innervation is still far from being definite and precise. Concerning many points we are still standing on the threshold of an almost unknown territory, a field in which there are only a few widely separated landmarks. We do not even know the nature of the most efficient sensory mechanism in the skin—pain ; we are unaware as to whether this pain mechanism is different from those underlying other forms of sensation, we do not know which tissues are supplied with a pain apparatus, whether it is the same in them all, or whether it responds to a different stimulus in different tissues (Waterston). It is obvious that in the skin the afferent nervous system, giving rise to sensations of touch, pain, cold, heat, pressure, and tension, will play a most extensive and important part in the establishment of our relations with the surrounding



world, and its peripheral organization will be the most complicated. And yet we know very little about it.

We know that the afferent nerves in the dermatomes of the skin are arranged segmentally, and that they overlap; we also know that the sympathetic nervous end-formation in the skin is non-segmentally arranged (Laruelle); a whole series of very delicately built and complexly constructed sensory end-organs and delicate nerve networks of sympathetic origin are well recognized. But of the function of these endings, their distribution, the way in which they disappear or are altered by skin diseases, their mode of regeneration after they have been destroyed by section or skin disease, we know very little. And yet these things are of fundamental importance, not only to further our knowledge of the normal histology of the skin, but foremost to increase our knowledge regarding the nature and origin of the symptoms in the different skin diseases we have to study.

It is known that in the skin there are heat spots, cold spots, pain spots, and touch spots; mechanisms for the appreciation of the very delicate sensations of light touch and other weak stimuli; and mechanisms which record crude ill-discriminated dull sensations. We can observe curious alterations in the mode of secretion of sweat and sebaceous material in the skin which must be caused by impulses travelling in the sympathetic nervous system. These alterations we would like to bring into line with alterations in the sympathetic nerve plexus in the skin, blood-vessels, and subcutaneous connective tissue. However, our information about all these things is still imperfect and uncertain.

We know that the skin has distinct tactile spots, that there must be receptors which permit recognition of differences in pressure and tension, but in other

places even a very light touch does not produce a tactile sensation, but gives rise only to the impression of sharp pain. We possess very definite and clearly localized heat and cold spots, as has been mentioned already. On the other hand, while it is impossible to arouse the sensation of touch in the cornea of the eye, the slightest stimulus produces a sensation of pain. This difference between touch- and pain-sensation seems to be of a secondary nature ; one may be absent, whilst the other is still present ; clinically we often find analgesia without anaesthesia. Physiologists, Blix, von Frey, and many others, have described very fully the numbers and distribution of the hot and cold spots and have laid stress on so-called punctate sensibility, the punctiform arrangement of sensation in the skin. Waterston finds that during a single examination a number of heat and cold spots could be defined and located, and that in this sense the punctate theory of sensation is true, but that a single examination does not reveal the whole truth. Repeated examinations of the same area of skin show that the number of spots from which a sensation of heat and cold can be elicited is immensely greater than that found at any one observation (Waterston, 1923). Stopford, however, denies this observation.

The cornea of the eye gives only the sensation of pain, the conjunctiva surrounding it possesses chiefly cold spots. But what do we know about the anatomical substratum for these physiological observations ? According to Waterston, special nerve organs and fibres cannot be postulated for each different sensation. Histological examination by serial sections of pieces of skin, where heat or cold spots had been located by clinical tests, has until now failed to demonstrate anatomically distinct and specific end-organs for the different elements of sensation (Stopford). We will return to and discuss this point later.

Von Frey believes that there are probably anatomically distinct end-organs for the perception of cold, but not for the perception of heat or pain. According to his theory, the outcome of laborious and extensive researches, the end-bulbs of Krause are responsible for the sensation of cold. Their presence in abundance in the conjunctiva, and, according to the observations of Belonoschin (1933), in the skin of the mammary gland, where many cold spots were located, seemed to prove his conclusions. However, when we put our very cold hands, in which there are no end-bulbs of Krause to be found, into a stream of hot water, the only sensation we get is that of increased cold, not a sensation of heat. If the temperature of the water is increased gradually, the sensation of cold also increases until it changes all at once to a sensation of pain, when the water becomes so hot that it in fact burns. The sensation of heat is always absent. On the other hand, the investigations of Holman (1936) have demonstrated that when patients with thermo-anaesthesia are put into a hot bath they then locate a feeling of heat even in the anaesthetic areas of their skin.

The intra-epithelial nerve-terminals in the epidermis may be concerned with the lightest forms of touch and the corpuscles of Meissner with tactile pressure. According to Adrian (1926, 1929) the encapsulated corpuscles of Pacini respond to even the slightest degree of pressure and to the movement of a neighbouring joint, but not to changes in temperature.

The corpuscles of Ruffini in the connective tissue of the skin are apparently associated with the perception of alterations in pressure and tension of the connective tissues of the skin; the corpuscles of Golgi-Mazzoni respond in the same way for the tendons and ligaments.

We know that the delicate nervous networks surrounding the roots of the small hairs are extremely

sensitive to slight movements of those hairs, so that hairs are to be looked upon as very delicate sensitive end-organs for touch. The intra-epithelial nervous nets of Langerhans may respond to stimuli aroused by destruction of the epithelium by force or by disease. But we do not as yet know anything about the anatomical substratum for the perception of cold and heat, nor, in spite of the interesting researches of the James Mackenzie Institute and especially of Waterston, of the mechanism underlying the perception of pain. According to Achelis (1936) pain is not conducted but only provoked. According to Waterston, not only are we ignorant as to the tissues from which pain can be aroused, but we are also ignorant about the nature of the receptors and the peripheral pathway by which the impulses travel which give rise to the sensation of pain.

We are also entirely ignorant of the position of any 'cortical area' associated with pain perception, nor do we know whether such an area even exists. The thalamus alone is possibly sufficient for the appreciation of pain sensation (Waterston, 1933, p. 3). So-called 'thalamic pain' indicates that pain may arise without peripheral stimulation, and thus sensations arising from the stimulation of end-organs registering pain may have a thalamic basis.

On the other hand, Ranson has shown (1934) that the hypothalamus is intimately connected with the sympathetic system, and that its stimulation produces all the signs of intense emotional excitement, which may find expression in fear, rage, and even in the feeling of bodily pain. But how, then, do we account for punctate sensibility, for pain spots, and for the varying intensity of pain? Is this possibly a cortical function?

The uncertain results of 'chordotomy', made known by the pre-eminent investigations and operations of Foerster, have shown how little we yet know concern-

ing the localization of pain-sensations. According to many observers nerve-fibres are separate; according to others (Orbeli, 1936) this is not at all certain: it is quite possible that whilst a mild stimulus gives rise to a sensation of touch, a stronger stimulus applied to the same nerve-fibre, an 'over-stimulus', gives the sensation of pain. According to Waterston, common experience seems to support such a view, but closer examination shows that this theory of over-stimulation cannot be supported, and that in the skin, at least, the pain apparatus is distinct and separate from that of touch.

It is known that in certain positions in the spinal cord are found homo-lateral fibres conducting the impulses aroused by tactile stimuli; in other positions are hetero-lateral decussated tracts registering pain impulses derived from the same skin area. In the cord a lesion in the lateral columns may affect pain, heat, and cold separately, leaving the other sensations unaffected, or the disturbance may be confined to two, or affect all three of these forms of sensation.

Thus, in the cord the fibres transmitting these three forms of sensation occupy separate positions within the lateral spino-thalamic tract (Stopford). It is obvious that this is only possible if the three types of sensation are conducted by three different sorts of fibres having a different origin in the skin, i.e. from dissimilar sensory end-organs.

But which of these different end-organs subserve the several sensations? We have already mentioned that from the cornea of the eye it is impossible to arouse the sensation of touch, the slightest effective stimulus producing only a sensation of pain. According to histologists the cornea possesses only intra-epithelial nerve-endings of the free-ending type. Do these subserve the sensation of pain?

If so, how can this be brought into harmony with the recent observations of Waterston, that in the skin (where we have a very extensive intra-epithelial nervous network of Langerhans) the passage of the point of a needle through the epidermis (i.e. through the epithelium) is entirely painless, and that it is possible to shave off a layer of epidermis from the tips of the fingers, and, indeed, to cut through the entire thickness of the epithelium, without causing any pain, in spite of the fact that the endings of the nerves conveying tactile sensation are divided in doing so, including the so-called tactile cells of Merckel?

It is only when the corpuscles of Meissner inside the connective tissue of the corium are sectioned by the razor that there arises a sensation of pain (Waterston, 1933). We thus meet with contradictions at every step.

According to Waterston (1933) the passage of a needle through the wall of an artery causes sharp pain, localized and acute, and he mentions that Professor Adam Patrick has noticed that a momentary prick is felt when a needle touches the wall of a vein in doing intravenous injections, so that even the walls of a vein must have sensibilities of their own. On the other hand, it has been concluded by Stürup and Carmichael (1935) that the periarterial plexus in man does not serve as an afferent pathway for pain from the periphery, a conclusion arrived at by Woollard and Philips (1932), Davis and Pollock (1930, 1936), Leriche (1935), and Moore and Singleton (1933). Thus we see that even the registration of pain from the wall of the blood-vessels is still doubtful, and that the whole problem of pain sensation is still far from being solved. The same may be said about the anatomy of the dull, so-called protopathic, and the sharper localized epicritic sensibility of Head as we shall see later on. Many of the points mentioned above will be discussed more fully in

the following pages. I have called attention to them here in order to indicate briefly how our existing knowledge of these fundamental problems lacks certainty and precision.

Any attempt to elucidate these problems may therefore be of value, and we may agree with Orbeli and his host of Russian collaborators (who in 1936 devoted a whole conference of the Russian Society of Neuropathology to them) that the study of degeneration and regeneration of the skin and of its different nerve-endings is of primary importance. It is for this reason that I deal with these phenomena first.

Our knowledge of the regenerative process in the skin, and especially in the nervous end-corpuscles, is still very superficial and restricted. We may cite here the papers by Werber and Goldschmidt on the regeneration of the sensitive corpuscles of Grandry and Herbst in the beak of the goose (1909), following an earlier paper by Gasiorowsky in 1901; the papers by Cajal (1921), Nasorow (1922), Kadanoff (1926), Marc Klein (1930, 1932), Sasybin (1930), and the Russian school (Girgolaw, 1921-6, Polissadowa, 1925, Kolossow, 1926, Plitas, 1926) who are cited by Sasybin, but who unfortunately published their results in the Russian language only, finally the papers by myself and Dijkstra (1932, 1933) and by Jalowy (1936). In these studies the regeneration of the end-corpuscles in different animals, including man, was investigated after cutting the nerves, after removal of a piece of the skin in which they are lodged, or after transplantation of pieces of the skin into other regions of the body.

In this chapter I propose to describe, more or less in detail, the results of some investigations on these points made both in our own and in other laboratories.

*Firstly*, that there exists a correlation in the organism between the amount of sensitive skin and the number

of nerve-cells and nerve-fibres innervating it is a fact well known in anatomy and established beyond any doubt.

That nature tries to re-establish this harmony when it is lost was demonstrated very elegantly by Detwiler and his collaborators during the course of some experimental embryological investigations. When spinal nerves in an amphibian embryo are brought into relation with a transplanted limb, they not only have a greater integumentary area to supply, but as Detwiler said, 1936, 'it is reasonable to expect that there should be an augmentation in the number of proprioceptive fibres to the muscles, but since it is impossible to distinguish between exteroceptive and proprioceptive neurones in larval ganglia, in limb-transplanting experiments it was impossible to determine what percentage of cell decreases or increases was due to alteration in the surface of skin and how much to alteration in the volume of muscle'. But by grafting two embryos together parabiotically in an ingenious manner it was possible to bring about a considerable skin loss without a corresponding muscle loss (Detwiler, 1926). When comparing the cellular losses it was shown that 60 per cent. of cellular losses in the spinal ganglia was due to skin loss and 40 per cent. to reduction in the volume of the muscles. Results pointing in the same direction were obtained when the volume of the skin was very slightly altered together with a marked muscle loss. The innervation of the enlarged or diminished areas of skin remained as far as possible in harmony with the extent of skin to be innervated.

*Secondly*, in order to show how great may be the increase or decrease in the number of sensory nerves in the skin of full-grown animals subjected to irritation or disease, I record here the investigations of Julius in the histological laboratory in Leyden (1926). When



he was studying the effects of tar on the skin of mice in relation to cancer problems he saw, a few weeks after he had begun painting tar on the skin, that there was not only the usual hyperkeratosis, loss of hairs, and

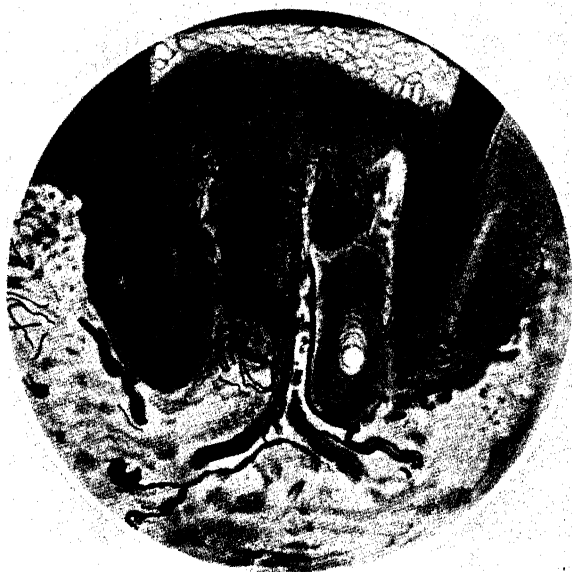


FIG. 1. 'Hyperneury' of the roots of the hair during the initial stage of tarred skin of the mouse. After Julius, 1926.

subsequent formation of a true cancerous tumour in the skin, but in the course of these weeks he found an exuberant proliferation of the nerve-fibres in the area of skin affected, especially in the connective tissue, surrounding the roots of the hairs (Fig. 1), and immediately beneath the epithelium. The nerve-fibres showed the peculiar lavish proliferation characteristic of fibres in the first stages of regeneration following nerve section. There was no trace of preceding degeneration, but Julius admits that this proliferation of the nerve-fibres, which was often accompanied by a clearly

marked 'katatropism' of the fibres on reaching the epithelium (Fig. 2) (exactly as I described twenty years ago (Boeke, 1916) in cases of heterogenic regeneration after connecting a motor nerve with a sensory



FIG. 2. 'Hyperneury' of the tarred skin of the mouse with 'katatropism' of the nerve-fibres when reaching the epithelium. After Julius.

nerve), must be at least partly the effect of a kind of regeneration process. In due course this proliferation of the nerve-fibres was followed by a marked degeneration and denervating process, and when a cancerous tumour had developed it turned out to be nerveless, every trace of nerve having disappeared from the affected skin-area. This strongly marked initial proliferation of the nerve-fibres under the influence of the chemical stimulus is interesting not only for the problem of the evolution of cancerous tumours, but also from a general point of view. It develops swiftly in the first

few weeks after the beginning of the experiment, and one might ask whether this proliferation of the nerve-fibres in the skin might not play a part in some of the skin diseases, in inflammation, in eczema, and so on.

There is a new field to be explored here and we do not know where the exploration of it will lead us, because the origin of so many of the skin diseases is still unknown. What is the role of the nervous apparatus of the skin during the development of such a disease, and above all what is the role during the healing or recovery process?

In the *third* place I would call your attention to the degeneration and regeneration of the nerve-fibres in the organ of Eimer in the snout of the mole (*Talpa europaea*) during the course of its development, which I described some years ago (*Innervationsstudie*, II, 1933).

This so-called organ of Eimer in the snout of the common mole (Fig. 3) is, indeed, the most interesting, the most simply built, and the most efficient sensory organ known. It is composed of about 5,000 papillae lying in a dense mass in an area of about 25 sq. mm. Each papilla contains a large number of nerve-endings, four to five tactile disks, together with at least one Pacinian corpuscle of simple structure in the connective tissue underneath each papilla and several less conspicuous end-organs of the character of Ruffini corpuscles (see Fig. 3, section through a normal papilla). Each papilla consists of a cylindrical column of epithelial cells with a broader base. Around the column running straight upwards as far as the horny layer are fifteen to twenty nerve-fibres, a single nerve-fibre passing up in the axis of the epithelial column. As soon as these fibres are well up in the epithelium they form little neurofibrillar expansions (Fig. 3), which become finer and more distinct in their further course towards the

horny layer. They pass to the axial side of the marginal fibres and come to lie inside the epithelial cells of the upper part of the column, being connected with

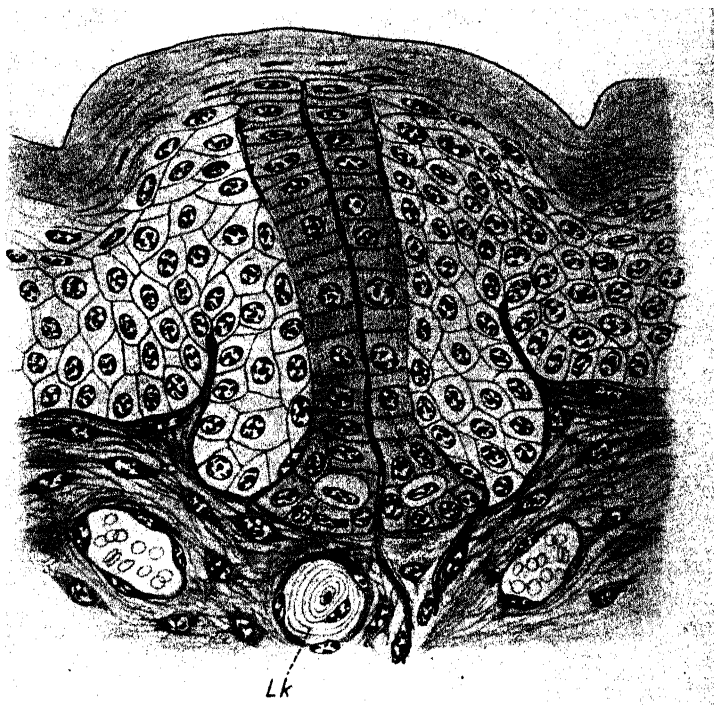


FIG. 3. Median section through a papilla of the normal organ of Eimer in the snout of an adult mole. After Boeke, 1933. Lk = lamellated corpuscle.

the marginal fibres by means of a very small and short stalk.

Thus there are formed in this small area of 25 sq. mm. more than 150,000 nerve-endings. This organ, which is very sensitive to touch, pain, cold, heat, moisture, &c., takes the place of the lost eyes of the animal and develops only after birth.

At birth it is composed of a number of small epithelial thickenings devoid of nerve-fibres. After birth the

young mole grows very rapidly and the organ of Eimer is developed within two weeks. A curious phenomenon then takes place.

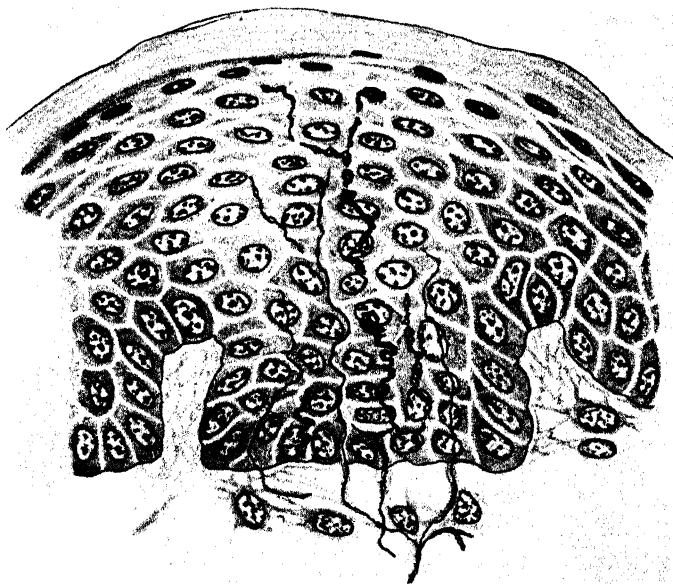


FIG. 4. Papilla of the organ of Eimer of a young mole of  $1\frac{1}{2}$  weeks with commencing degeneration of the primary innervation.

The epithelial papillae of the newly formed organ do not contain as yet the column of the cells described above. The nerve-fibres are scattered throughout the epithelial papilla without any distinct arrangement (see Fig. 4). They enter the epithelium at different points and cannot be distinguished from the other nerve-fibres beneath the epithelium forming the network of Langerhans. The corpuscles of Pacini are beginning to develop. Quite suddenly in the course of the third and fourth week of the independent life of the young animal the cells of the epithelial papillae

of the organ of Eimer start to move, they change their positions, without mitoses, and arrange themselves into the regular columns described above (compare Fig. 4

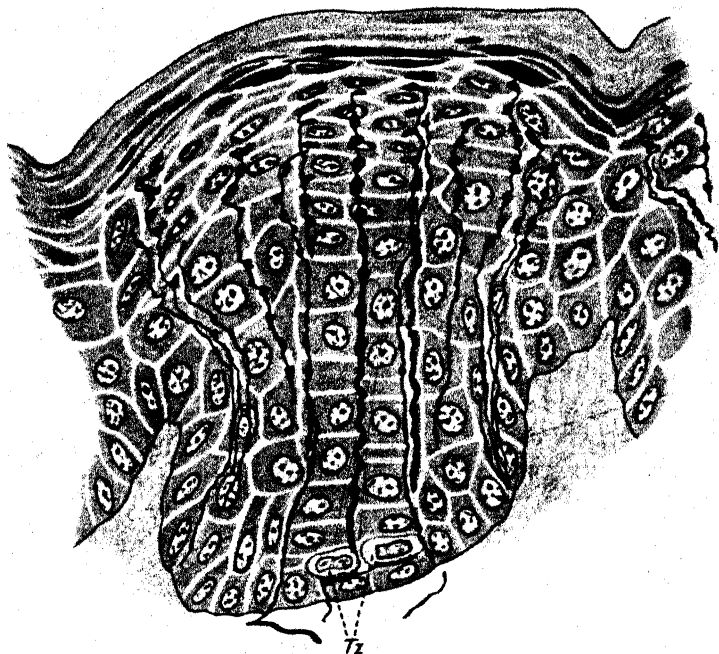


FIG. 5. Papilla of the organ of Eimer of a young mole of 3 weeks, with advanced degeneration of the primary nerve-fibres and the beginning of the formation of a central cylinder of epithelial cells with definite innervation.  
*Tz* = tactile cells of Merkel.

with Figs. 5 and 3) and thus the definite form of the adult organ is acquired.

During this rearrangement of the epithelial cells the nerve-fibres which lay inside the epithelial papilla can be seen degenerating, crumpling up, so to speak (see Fig. 4), and disintegrating into small drops of neurofibrillar substance as in degeneration after nerve section.

An entirely new innervation is now formed, new nerve-fibres can be seen growing up into the epithelium in a definite pattern (compare Fig. 5 with the cross-

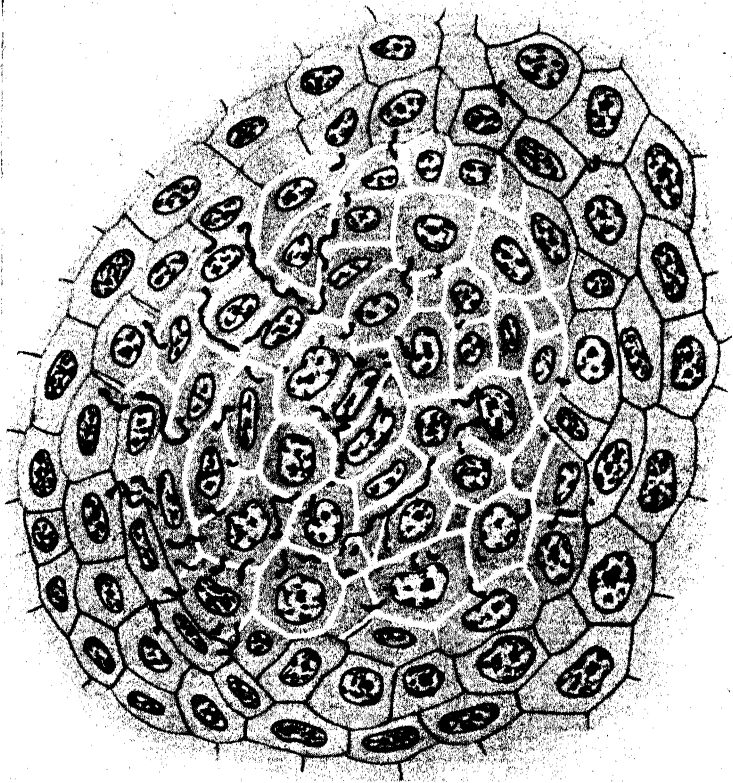


FIG. 6. Cross-section through the central part of a papilla of the organ of Eimer of a young mole of 7 cm. length with primary innervation.

sections of Fig. 6 and Fig. 7), and in the course of those few weeks the innervation, described for the adult organ, develops. After this the organ remains unaltered throughout life; apparently it has now reached its final form. What seems to be the most interesting feature of this mode of development is the rapid re-

arrangement of the epithelial cells into a column, and the rapid and complete degeneration and destruction of a set of apparently entirely healthy nerve-fibres and

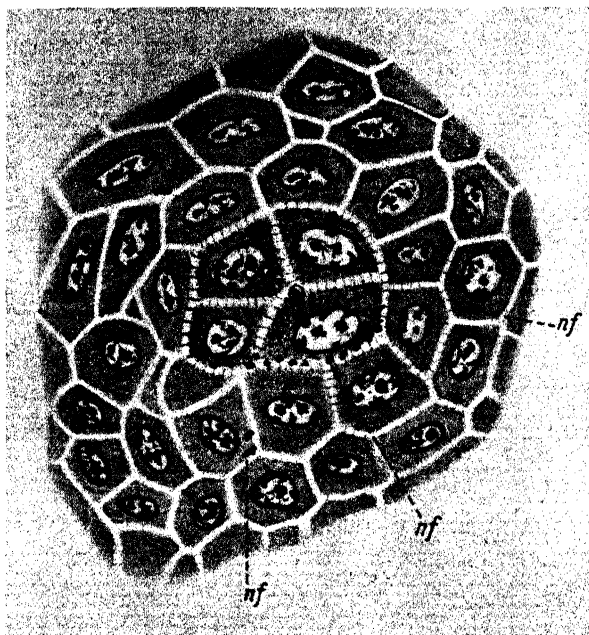


FIG. 7. Cross-section at the same level through the central part of a papilla of the organ of Eimer of an adult mole with central cylinder of epithelial cells and definite innervation. *nf* = nerve-fibres.

their replacement by a set of newly formed fibres, in the course of normal development. Something of a similar kind has been described in other cases, but it has always been doubted, because it seemed to be a process entirely foreign to a normal development.<sup>1</sup> Here we see it demonstrated as a feature of normal development *ad oculos*, there being no shadow of doubt as to its normality.

<sup>1</sup> According to Bluntschli, Da Costa, and other embryologists degeneration of cell-complexes in order to attain another form of embryonic tissue is a feature of normal development.



Before turning to the question of degeneration and regeneration of nervous end-organs in the human skin, I want to discuss the question as to whether entirely



FIG. 8. Photograph of duck's bill containing two pieces of transplanted 'scaly' skin of the foot.

After Dijkstra, 1933.

new sensory corpuscles are formed during the process of nerve regeneration in the skin. We will discuss this question later on for the human skin. Here I want to describe some experiments made by Dr. Dijkstra in my laboratory on the regeneration of the skin and its sensory endings in birds and animals in which we may study these endings with exceptional clearness.

The problem was attacked in two ways: firstly by the usual method of cutting the nerves and studying their degeneration and regeneration in the intact skin, and secondly by the method of cutting away a piece of the entire skin with its connective tissue, and then either letting new skin heal over the defect or transplant-

ing into the wound a piece of skin removed from the same region (homo-transplantation) or from another region of the skin of the same animal (hetero-transplantation, Fig. 8).

In the soft leathery skin covering the bill of ducks and geese, and in the mucous membrane of the palate and of the tongue of a number of waterfowl, there are found a large number of very regularly built lamellated tactile corpuscles, the corpuscles of Herbst and also

the sensory end-corpuscles of Grandry. These are composed of two or more thick flattened cells, enclosed in a common capsule of connective-tissue cells, with the axis-cylinder of the entering nerve-fibre terminating between them in a flattened expansion, the tactile disk. These end-corpuscles are of an astoundingly simple, almost diagrammatic form.

The corpuscles of Grandry degenerate after the cutting of the afferent nerves, as do the corpuscles of Herbst, but the former regenerate much more easily, as was demonstrated by Marc Klein and Dijkstra.

From a general point of view the phenomenon discovered by Dijkstra is interesting. He found that during the process of regeneration of the nerves following degeneration after cutting of the afferent nerve-fibres, a number of new Grandry corpuscles are developed in addition to the regenerated old corpuscles. Of these newly formed end-corpuscles some degenerate and disappear after a time, but others develop into full-grown permanent corpuscles of Grandry. The lamellated corpuscles of Herbst regenerate too, but no new ones are formed, as far as could be seen.

Of far greater interest is the regeneration of the end-corpuscles after the removal of a piece of the entire skin. Marc Klein (1930, 1932) cut off the point of the bills in very young birds and found regeneration of the corpuscles of Grandry, but not of Herbst, in the scar tissue. Dijkstra (1934) took away one square centimetre of entire skin with connective tissue down to the periosteum. The wound healed perfectly, the new skin being hardly distinguishable from the normal skin surrounding the wound. There was no retraction. In a transverse section the line separating the newly formed tissue, the epithelium and connective tissue, from the underlying periosteum was distinctly seen. In the newly formed connective tissue not only had

the nerve-fibres regenerated from the central stump of the cut nerves of the surrounding tissue, but corpuscles of Grandry and Herbst had formed in such

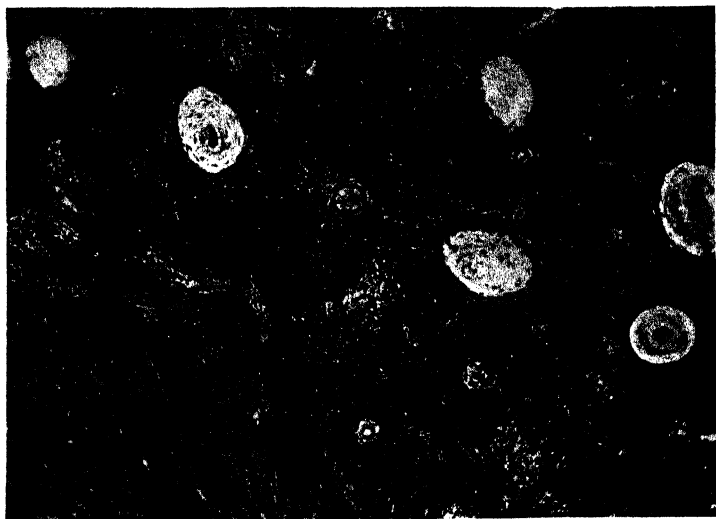


FIG. 9. Tangential section through the regenerated skin of the duck's bill with newly formed sensory corpuscles of Grandry and of Herbst, after removal of the entire skin. After Dijkstra.

large numbers as to parallel those in the normal skin surrounding the scar ; indeed in the beginning a greater number were formed (see Fig. 9, tangential section of totally regenerated skin), but just as in the case of regeneration after nerves have been cut, a proportion of the newly formed end-corpuscles degenerate after a time, until at the end of about eight to ten months an approximately normal and stable condition has been arrived at.

The development of these new corpuscles in the newly formed connective tissue follows exactly the same course as that described some years ago by Heringa during embryonic development. Their disposition in the newly formed skin is almost as regular as in the

normal skin. The corpuscles of Herbst appear a little later than the corpuscles of Grandry, but quite as regularly. I described the same phenomenon—an initial exuberant regeneration and a subsequent degeneration of a number of the nerve-endings until a stable condition is reached—twenty years ago for motor-endings in the muscles of the tongue. It seems to be a feature of general occurrence. It may be compared with the initial exuberant outgrowth of the nerve-fibres of the skin in the experiments of Julius mentioned previously.

Another very interesting experiment was made by Dijkstra. A piece of the skin of the bill was transplanted on to the foot and vice versa. The skin of the feet and legs of these birds is far less abundantly innervated than the skin of the bill, the corpuscles of Herbst and of Grandry being but rarely found, often being entirely absent. When we transplant a piece of the scaly skin of the foot on to the bill, taking care that the pieces transplanted are as nearly as possible of the same size as the wound, they heal very well in their new surroundings. They remain alive and during growth retain their macroscopic features unchanged (see Fig. 8). Thus the scaly appearance of the piece of the skin of the foot transplanted into the bill remains even after twelve months, and a piece of the skin of the bill transplanted into the foot or into the leg remains as smooth as it was in the beginning of the experiment.

The nerve-fibres grow out from the surrounding tissues nearly as quickly and as well as after simple section of the nerve-fibres, and after a time the transplanted piece of skin is as full of regenerating nerve-fibres as in the other experiments.

But what interests us here particularly is that in the skin from the foot (where, as we mentioned already, the corpuscles of Grandry are almost entirely absent),

no new corpuscles are formed even by the ingrowing nerve-strands coming from the skin of the bill, whilst in the skin derived from the bill and transplanted on the foot, newly formed and regenerated corpuscles of Grandry are found in great numbers.

Thus we find, contrary to the conclusion which Kadanoff drew from his transplantation experiments (transplantation of the skin of the sole of the foot into the snout and vice versa in *Cavia*), that the newly regenerated nerve-endings are formed to correspond with the surrounding tissues, into which the nerve-fibres are growing out when regenerating (*herkunftgemäss*), and not to conform in type to those previously present in the tissue surrounding the nerves normally at the place where they come from, growing out to the piece of skin with degenerated nerves (*ortsgemäss*). This shows that in regeneration even the regenerating nerve-fibres are entirely under the influence of the surrounding tissue when the new sensory corpuscles are being formed.

This finding seems to me to be of fundamental importance for forming a conception of regeneration processes in nerve-fibres. A nerve-fibre of the skin of the bill regenerating and growing into a piece of skin of the foot is not able to build there corpuscles of Grandry as it does when it grows into a piece of the skin of the bill. A nerve-fibre of the skin of the foot growing into a transplanted piece of the skin of the bill is able to form there the corpuscles characteristic for the skin of the bill, although in the skin where these nerve-fibres come from, no such corpuscles are found. It seems that a differentiation *in loco* plays a definite part in these regeneration processes, just as I held was the case for the regeneration process in the organ of Eimer mentioned above (Boeke, 1930).

Even though the foregoing experiments throw some

light on the question of the regeneration of the sensory elements of the skin, the problem which interests us chiefly is the question of sensibility of the human skin; what are the structures concerned, what is the part played by the sympathetic, how are they affected by degeneration and regeneration, and how does the human skin and the nervous elements respond to destruction of function by disease or wounds?

As I pointed out in the introductory remarks to this subject, histology has sadly lagged behind in this aspect, and as was quite natural physiologists and neurologists on the whole have left the different kinds of sensory perceptions alone, and restricted themselves to a study of only the physiological side of the question.

A consequence of this method of study was the sensory theory of Head, conceived and published in 1905 and 1908, and widely known and accepted in the realm of neurology. As it is so well known, I need only describe it in a few brief terms.

To study the relationship between anatomical recovery of nerves and nerve-endings during regeneration after section of an afferent nerve and the return of the different qualities of sensation, it is necessary that the patient be a trained observer and that the injury be determined beforehand. To fulfil those demands, one of the cutaneous nerves of the left arm of Head himself was sectioned in the neighbourhood of the elbow, and the ends were united again with silk sutures. Before the operation the sensory condition of the arm and back of the hand was minutely examined, and the same was done during the regenerative process. The mode of recovery of sensation after this injury led Head to conclude that there are different types of sensation which depend upon separate systems of peripheral nerves and endings. Firstly the protopathic nerves, sympathetic nerve-fibres, which provide us with that

curious, uncritical, poorly localized sensibility, which returns during the first phases of recovery after section of the nerve. Secondly, those nerves which are directly associated with motor impulses and pressure, and govern deep sensibility. Thirdly, those nerve-fibres which end only on the superficial tissues, which are connected with the different forms of end-organs described above, and which give us the sharply defined, exactly localized sensations to light touch, temperature, and pain, the epicritic nerves. According to Head, these regenerate more slowly than the protopathic fibres.

This theory, which has been of great value in advancing neurological conceptions, may be characterized by the following quotations from the publications of Head and his collaborators:

‘The whole body within and without is supplied by the protopathic system. The fibres of this system in the skin may be spoken of as somatic, those to the internal organs as visceral protopathic fibres. Thus we shall no longer speak of the afferent sympathetic system, but of the protopathic supply of the internal organs.

‘Another set of afferent fibres peculiarly associated with the impulses of movement and pressure exists in connection with the pacinian organs. In the body and limbs an analogous system is found peculiarly susceptible to pressure, to the localisation of movement and to the appreciation of position. The fibres of this system run in conjunction with the motor nerves.

‘In addition to these two systems, which are distributed to all parts of the body within and without, the surface of the body only is supplied by a third system, which we call epicritic. This endows the skin with sensibility to light touch. To the impulses conducted by this system we owe the power of localising the position of cutaneous stimuli, of discerning the doubleness of two points, and of discriminating between minor degrees of heat and cold, and other special attributes of sensation. The fibres of this system are more easily injured, and regenerate more slowly than those of the protopathic

system. They are evidently more highly developed, and approach more nearly to the motor fibres that supply voluntary muscle, in the time required for their regeneration.' (*Brain*, vol. xxviii, p. 114.)

In the following quotations this view is sharply formulated:

'The afferent fibres in the peripheral nerves can be divided into three systems. 1. Those which subserve deep sensibility, and conduct the impulse produced by pressure. The fibres of this system run mainly with the motor fibres and are not destroyed by division of all the sensory nerves to the skin. 2. Those which subserve protopathic sensibility. This system of fibres and end-organs responds to painful cutaneous stimuli, and to the extremes of heat and cold. It also endows the hairs with the power of reacting to painful stimulation. These fibres regenerate rapidly after the ends of the nerve have been reunited; if the operation has been successfully performed, sensation begins to return within from seven to ten weeks. In any peripheral nerve the distribution of protopathic fibres usually overlaps greatly the area supplied by the fibres of the adjacent nerves. 3. Those which subserve epicritic sensibility. The nerve fibres and end-organs of this system endow the part with the power of responding to light touch with a well-localised sensation. The existence of this system enables us to discriminate two points and to appreciate the finer grades of temperature called cool and warm. These fibres regenerate more slowly than those which subserve protopathic sensibility after reunion of a divided nerve, and sensation does not usually begin to return in less than six months under the most favourable conditions. The distribution of these fibres in the larger peripheral nerves, such as the median and ulnar, overlaps little compared with the great overlapping of the protopathic supply.' (Loc. cit., p. 298.)

'What we have called "protopathic" and "epicritic" sensibility depend on two anatomically separate systems of fibres and end-organs.' (Loc. cit., p. 291.)

I have quoted this theory verbatim because of its extreme lucidity and importance, and because it has



played such a large part in subsequent neurological discussion. It meant the beginning of a new era in neurology, because in it were expressed so very clearly the difficulties every neurologist felt, and the solution appeared so clear and simple. We find this theory discussed throughout the literature on skin sensation and its recovery after nerve section following these publications. The theory has either been accepted (as for instance in recent years by Stopford, 1930) or rejected (Boring, 1916; L. L. Pollock, 1920; Frasier and Silbert, 1920; Loyal Davies, 1934, 1936; Moore and Singleton, 1933; Leriche, 1935). An anatomical investigation, however, of regenerating nervous end-organs themselves and a study of their histological features during the recovery of sensibility have not followed on the publication of the physiological basis of the theory; after all, that is what we needed, for without a solid anatomical basis, the physiological theory must needs remain a castle floating in the air.

The names epicritic and protopathic sensibility are perfect, and the description given by Head of these two forms of sensation remains unequalled. Neurologists have used these names for the two kinds of sensation found so often after injuries of the cutaneous nerves and will continue to use them everywhere at all times. They will always remain useful and unchallenged.

But the question which interests us here, is whether protopathic sensibility depends upon an anatomically separate system of fibres and end-organs of a sympathetic nature, as maintained by Head; or upon the same system as epicritic sensibility, only working under different conditions.

Now, as mentioned already, the part ascribed to the sympathetic system in cutaneous sensation has been severely criticized in recent years. The so-called sym-

pathetic fibres of Timofeew, surrounding the sensitive corpuscles of Meissner, have been shown by Lawrentjew (1936) to be of somatic nature.

That the sympathetic nervous system has an influence on the sensibility of the skin has been shown by Orbeli, who observed modifications in the latent period in reflexes on the side, in which sympathetic rami communicantes had been severed. The sympathetic plexus surrounding the sensory corpuscles, which, as I hope to show you later, has nothing to do with the apparatus of Timofeew, mentioned above, is purely of an efferent nature and appears to have nothing to do with sensation.

But even if we admit these things, independent protopathic sensation of a sympathetic nature is quite another problem. It has been denied by a number of investigators. Protopathic sensation does not remain intact after injury; sensation disappears entirely, and protopathic sensation appears to be only the first symptom of the regeneration process. Consequently nerve-fibres subserving protopathic sensation must have been divided by the sectioning of the cutaneous nerves. They must have their own end-organs. Now, it is true that when a cutaneous nerve is sectioned, the sympathetic fibres running in it are also severed. But, as I hope to show you in due course, the sympathetic plexus in the mucous membrane of the tongue remains intact after the section of its somatic nerves. Even when the sympathetic fibres are severed, as in the case of Dr. Head, they are found to have nothing to do with sensation; they seem to be of a purely efferent nature. No trace of independent end-organs which could be held responsible for protopathic sensations has been found in this sympathetic end plexus. As I have mentioned already, even the apparatus of Timofeew, which is found lying inside the capsules of the corpuscles of

Meissner, and which hitherto has been generally supposed to be of a sympathetic nature, has been shown by Dogiel and later experimentally by Lawrentjew to be of a somatic nature.

Sensory phenomena, even of a crude nature, which reach consciousness are not evoked by the true sympathetic system, but seem to be in all cases of a somatic nature. It seems to me that we must look in another direction for the solution of the problem of protopathic sensation. In the first place we should inquire into the anatomical alterations occurring in the skin after injury.

This was first done by Dr. Heringa and myself in consequence of an unfortunate accident which took place in 1923. The entire ulnar nerve, including its dorsal branch, the ulnar artery, and the tendons of the ulnar muscles of Dr. Heringa's right hand were severed below the wrist. Within an hour after the injury the tendons and the nerve were sutured. The wound healed by first attention.

Both superficial and deep branches including the dorsal ramus of the ulnar nerve were completely divided. Investigation by Dr. Stenvers showed that the entire area innervated by the ulnar nerve was quite insensitive to light, touch, pain, and temperature, and the muscles of the ulnar side of the hand, including the adductor pollicis, were paralysed. After a lapse of several months sensation began to return and the affected area was again investigated by Dr. Stenvers, and the results mapped out with the utmost care. Subsequently a piece of the skin, together with the underlying connective tissue, was removed from the centre of the affected area, being on the borderline between the palm and the hair-covered back of the hand (December 1923). This was examined histologically in serial section after staining by the silver method. The sections were ex-

ceedingly well stained, and a very accurate examination of the nerve-fibres and endings was possible.

The study of the response to stimulation in the injured area by Dr. Stenvers showed that sensation was typically protopathic in nature. Light touch (cotton-wool) was hardly felt, stroking the hairs was very faintly perceived, a light pin-prick was entirely unappreciated, often a heavy prick was discriminated only after a prolonged latent period (one minute) and it then gave rise to radiating paraesthesiae, slowly followed by a somewhat better localized sensation of pain.

A heavy prick with a pin was often not appreciated as pain, but only as touch, especially in the area where the piece of skin has subsequently been excised. The patient believed that the head of the pin was being used rather than the point. Localization was very poor, the distance apart at which two simultaneously applied points of the compass could be discriminated as two, was about 6 cm. as against about 5 mm. in the same area on a normal hand. A further examination eight months after the excision of the skin showed that whilst in the normal hand the distance still remained at 4 mm., on the skin surrounding the scar in the injured area, the distance at which two points of the compass could be discriminated had now diminished to plus or minus 13 mm.

According to Dr. Stenvers's protocols, minor degrees of temperature change above or below that of the body produced no effect at all upon consciousness. Ice and hot water were appreciated as such, but the limits between which 'hot' and 'cold' were appreciated were somewhat narrower than those given by Head for typical protopathic sensibility. Minor differences of temperature (cool and warm) were not discriminated (December 1923 and January 1924). In the area from which the skin had been taken, water below 21° C.

usually gave the sensation of being cold, and water above  $38^{\circ}$  C. the sensation of warmth. In this same area before excision of the skin, water at  $18^{\circ}$  C. was appreciated either as 'cold' or 'warm' after a latent period of about four seconds. When temperatures of  $5^{\circ}$  C. and of  $24^{\circ}$  C. were used as contrasts,  $24^{\circ}$  C. was felt as 'warm'. A sensation of 'cool' easily obtainable on the normal side could not be evoked.

The following curious phenomenon, characteristic of the protopathic sensibility, was recorded. Pinprick was not felt as such, but when a sensation was produced by pricking it gave rise to an extremely unpleasant feeling which radiated widely over the affected area, immediately causing the patient to withdraw his hand. This finding corresponds exactly with Head's description:

'Closer examination of parts in this condition (viz. protopathic sensibility) shows that, although the hand has become sensitive to pain and temperature, this sensibility is strangely altered. A prick is appreciated, but produces a sensation that radiates widely over the affected area. It causes unnatural discomfort, and the patient has an uncontrollable desire to withdraw his hand.' (Head, l.c., p. 101.)

I have quoted these observations at some length because they seem to fit very well into the explanation which histological examination of the sections seems to offer us, and not into Head's original hypothesis that protopathic sensation is sympathetic in nature.

Histological investigation of the excised piece of skin showed us, firstly, that sympathetic nerve-fibres were present everywhere, but whether the number of fibres present was normal or not, could not be determined. It is always exceedingly difficult to make observations on sympathetic fibres of a statistical nature which have even the smallest value. One must be content to be able to state that they are present. Delicate nerve-fibres

were found alongside the blood-vessels; even around the walls of the sweat glands and their ducts delicate nerve fibrillae could be seen; here and there these seemed to be in connexion with the gland cells. As far as I could determine, these fibres were scarcer than in normal preparations of skin, but otherwise behaving in exactly the same way as in normal sections through the skin, i.e. without endings which could have been held responsible for even dull protopathic sensation. They showed the same peculiarities as in normal tissues.

In the somatic nerves, however, regeneration appeared to be taking place actively. Nearly all branches of the cutaneous nerves visible in the sections were filled with regenerating nerve-fibres, not only the larger branches in the deeper layers of the connective tissue, but even the medium-sized and fine branches in the superficial layers of the corium.

As far as could be determined, all the nerve-fibres were in a typical regeneration phase; showing the protoplasmic bands of Buengner: that is, being filled with a number of delicate neurofibrillar strands. Myelin sheaths did not appear to have developed. Even the sensory end-organs themselves were in full process of regeneration. Throughout the skin delicate black-stained neuro-fibrillar strands could be seen branching and dividing, forming small networks and loops, and running in different directions through the connective tissue of the sensory end-organs.

Not all the end-organs were regenerating, at least not all of them were in the same neurofibrillar phase. Among the tactile corpuscles of Meissner for instance, which were present in greater numbers than is generally recorded for this part of the skin,<sup>1</sup> were some

<sup>1</sup> This observation, which was made in 1923, is in accord with the later observations of Dijkstra, van Straten, and myself, here recorded.

which were still quite devoid of regenerating nerve-fibres. The end-organs of Ruffini and Golgi-Mazzoni, which could be recognized as such in the sections, were all found to have associated regenerating neurofibrillar strands (see Figs. 10 and 11).

In the epithelium itself regenerating nerve-fibres could be seen in only a few places. Whether more were present than those impregnated in the sections it is difficult to say, for intra-epithelial nerve-fibres are difficult to impregnate. Free-ending nerve-fibres in the epidermis seem to be very rare even in normal skin, leaving aside areas in which they are specially developed, i.e. finger-tips, snout of the pig or the cow, in the neighbourhood of taste-buds in the tongue, &c. However, it is still a fact that when we examine many pieces of impregnated skin, we occasionally come across a section in which intra-epithelial nerve-fibres are present in far greater numbers than usual.

Besides the innervation to the tactile end-organs, the nerves to the hairs were also regenerating. Here too, the regenerating nerve-fibres showed the same phenomena as in the other end-organs, that is, an irregular plexiform arrangement of the neurofibrillar strands; entirely unlike the rather regular arrangement of the terminal arborizations of nerve-fibres around normal hairs. In a few cases the regenerating nerve-fibres presented a more regular arrangement, similar to those innervating normal follicles.

In short, we found the somatic nerve-fibres throughout the injured part of the skin in full process of regeneration, in contrast to the sympathetic fibres, which, as has been mentioned before, were less frequently seen than in normal skin. Regarding the sympathetic fibres, there was no indication of the great increase in numbers of nerve-fibres found in the experiments of Julius, mentioned at the beginning of this lecture.

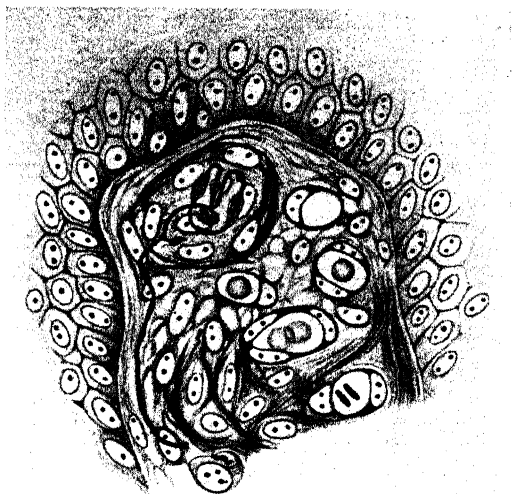


FIG. 10. Regenerated sensory corpuscle of Meissner after cutting of the ulnar nerve, human hand. After Boeke and Heringa, 1924.

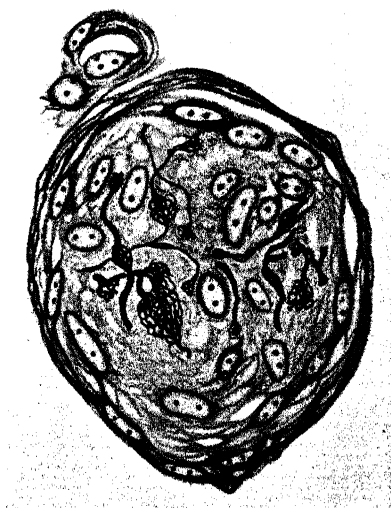


FIG. 11. Regenerating sensory corpuscle in the corium of the human hand, after cutting of the ulnar nerve. After Boeke and Heringa.



This result does not support Head's theory. For, when the regenerating nerve-fibres in the different sensory end-organs of the excised piece of skin are examined in detail the following appearances can be noted. There are ramifications, end-loops, and numerous flattenings and expansions, the latter being composed of fine networks of neurofibrils showing here and there distinct connexions with the protoplasm of the surrounding tactile cells. These appearances are highly suggestive that a distinct sensory function is being already exercised by these end-organs even though it is not yet complete. This being the case, it would seem to be more in accord with what we know of the clinical and physiological features of regeneration to regard these regenerating sensory end-organs as responsible for the curious dull, diffuse, widely radiating sensation which is unaccompanied by any definite appreciation of the position of the spot stimulated, that is, the protopathic sensibility of Head, than to regard the phenomena to be dependent upon the sympathetic protopathic nerves postulated by Head.

No one has been able to find these nerves, the existence of which is based only on physiological considerations. Thus in our opinion, protopathic sensibility is due to the stimulation of sensory end-organs and corpuscles, which are still in process of regeneration; the identical end-organs producing epicritic sensibility when completely restored to their normal condition.

It needs not to be emphasized here that, as Stopford has pointed out so clearly, during this regeneration process of the sensory corpuscles there is a disturbance and readjustment of the central connexions in the brain of the various cutaneous end-corpuscles, as the regenerating out-growing nerve-fibres will not always

establish relations with the type of nerve-ending with which they were previously connected. This readjustment of the central connexions in the cerebral cortex might in some degree be held responsible for the belated return of the epicritic sensibility (Stopford). But in the first place this will cause another type of beginning sensibility, not protopathic, but disorderly, and in the second place this readjustment seems to be established very quickly after the regeneration of the nerve-fibres in the various end-corpuscles (after crossing of the eye-muscles in monkeys, which causes a disturbance of the combined movements of the eye-balls, in the course of a few days, as was shown by the experiments of Marina). I do not think therefore that this disturbance and subsequent readjustment of the central connexions form a sufficient explanation of the two-stage recovery of cutaneous sensibility, as it is maintained by Stopford. The regeneration of the sensory end-corpuscles remains the chief factor in causing the protopathic sensibility in regenerative processes.

The curious widespread, radiating, unlocalized sensation may perhaps be due to the fact that during this stage of regeneration no isolating myelin-sheaths have yet developed (cf. Trotter, 1924), and the regenerating fibres are still running inside the protoplasmic bands of Buengner. As a rule myelin-sheaths, especially in the neighbourhood of terminal organs, only reappear in the last stage of the regeneration process. This hypothesis would seem to explain all the known facts concerning protopathic sensibility far better than that of Head. For instance, the following facts can be explained: the curious overlapping of the protopathic area and the area of true epicritic sensibility; the gradual recovery of the different forms of epicritic sensibility and many of the phenomena of loss of

sensation and recovery processes described so well by Stopford in his interesting book on *Sensation and the Sensory Pathway* (1930).

It explains the diminution of the protopathic area, the fact that the mere recognition of contact, of pressure, and the pain induced by excessive pressure recover at an earlier date than other forms of deep sensibility.

Many other phenomena also fit into this hypothesis far more easily than into the original hypothesis of protopathic sympathetic nerves. It also explains the well-known fact that recovery of sensation at a given point following suture of a divided nerve occurs gradually and not, as Head supposed, in all-or-none fashion. The experiments on overlap by Stookey (1922), Pollock (1919), and Sharpey-Schäfer (1928, 1930) did not agree with Head's hypothesis.

The experiments of Kredel and Evans (1933) did not support Head's hypothesis. They examined the return of sensation in a denervated skin pedicle, also in full-thickness pedicle flaps, Wolfe, Reverdin, and Thiersch grafts, in a number of patients. They made the following statement: 'a new and ideal terrain for following sensory return, since one has a completely denervated and a well demarcated area of anaesthetic skin into which new nerve fibres must find their way' (l.c., p. 3). In this material regeneration began only at the base of the graft, where it took root in the skin, and could be followed through different stages from the base of the graft to the surface. Their results could be entirely explained on the hypothesis of a gradual recovery of the different sense organs, which is seen in the regeneration process of the sensory nerves, causing the different forms of returning sensation so clearly described by Head and his collaborators.

These observations of Kredel and Evans appear to

be in full harmony with our hypothesis. With regard to the observations of Dijkstra mentioned above concerning the formation of entirely new end-organs in an area of transplanted skin, or in cases of ordinary regeneration, it is of interest that Kredel and Evans state that in several of their cases there was strong physiological evidence that cut nerves of the bed invaded a flap or pedicle independently of the old neurilemmal sheaths. In this way entirely new nervous paths and new end-organs may be formed.

In regard to these problems another method of studying the regeneration of sensory nerves in a newly formed piece of skin has been adopted by us in the course of the last two years, and I wish here to give a summary of these investigations, which are still in progress in my laboratory. The methods consisted in experiments on the regeneration of the skin of the finger-tips in a number of monkeys and in man.

When a nerve of the finger-tip is severed as was done by Jalowy in 1935, and the result studied, it is seen that the cut nerves and the different end-organs (i.e. nervous end-formations and tactile cells) degenerate. During regeneration the corpuscles of Meissner and other end-organs reform (cf. Jalowy, 1935), using as far as possible the old tactile cells. The regenerated end-corpuscles are thus found in the same spots as the original ones. The epithelial and papillary ridges of the skin of the finger-tips remain intact and retain their characteristic pattern, the distribution of the sensory end-organs remains the same as before the injury. Jalowy records a remarkable observation; a number of the tactile cells of Merkel degenerate, lose their innervating fibres, and transform into ramifying cells of Langerhans, which after a time in their turn degenerate.

When a piece of the entire skin of the finger-tip is

removed, i.e. the epidermis, the corion, and a portion of the subcutaneous connective tissue, the entire skin must regenerate, as in the experiments of Dijkstra on the regeneration of the skin in the duck's bill. In this way one is able to study the formation of new skin with new ridges, new connective tissue, and new sensory end-organs. We merely have to remove the newly formed piece of skin and to study it in serial sections.

This was done in a number of monkeys (*Macacus rhesus*) and on the finger of Dr. van Straten, one of my collaborators. He is making an extensive study of the material.<sup>1</sup> A piece of the skin and underlying tissue of the centre of the fingertip of the little finger of Dr. van Straten's left hand was removed by a skilled surgeon. The wound healed by first intention without becoming infected. The skin regenerated in about two months. A series of finger-prints taken at regular intervals showed the external features of the regenerating skin and its ridges. After the wound had completely healed the regenerated skin was examined with the utmost care by Dr. Stenvers. Pain spots, the sensation which was still vague and of a protopathic nature, and every other detail of the returning sensation were tested and mapped out on an enlarged scale as carefully as possible and the diagram photographed. After this the piece of skin was removed, hardened in formalin, &c., and cut into serial sections. It was thus possible to identify the smallest spot in the sections with the tested spot on the enlarged photograph; every spot tested physiologically could be identified in the serial sections. The impregnation of the sections turned out to be excellent.

<sup>1</sup> The results of this investigation will be published *in extenso* with many illustrations by Dr. van Straten and myself in the *Zeitschr. für Mikrosk. Anat. Forschung*.

In the monkeys the area of skin removed was somewhat larger, but even then the skin regenerated in a perfect manner; the area regenerated could scarcely be recognized. There was no inflammation. The re-

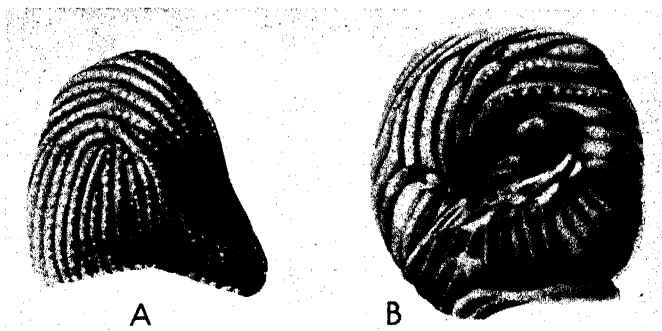


FIG. 12, A and B. Ridges of skin of finger-tip of *Macacus rhesus*.  
(A) Normal. (B) Regenerated after removal of the skin.

generating skin was at first entirely smooth, and it was only after two months that the new ridges began to show themselves. They first became visible at the periphery of the piece regenerated and then gradually approached the centre (Fig. 12, A and B). There was very little retraction of the tissues. As soon as this stage had been reached, a similar piece of skin was removed for the second time, photographed and drawn, hardened in formalin, impregnated, and cut into serial sections and studied. The pattern of the ridges was quite different from that of the original piece of skin (Fig. 12, A and B). Here, too, the impregnation turned out to be very good. In the cross-section of Fig. 13 through the centre of the regenerated skin the formation of the ridges and papillae is clearly visible.

In the first place it is interesting from a histological point of view that the epidermal ridges have com-

pletely regenerated and that the pattern visible after regeneration is not caused by tissue retraction but



FIG. 13. Transverse section through the centre of the regenerated piece of skin of finger-tip of Fig. 12B, *Macacus rhesus*.

by the formation of entirely new ridges in the area of smooth regenerated skin. Some retraction of the ridges is recognizable in the centre of the skin, but the ridges are of an entirely new pattern and their mode of development and the formation within them of new sensory end-corpuscles (Fig. 13) can be studied with great precision.

In the papillary ridges new sensory corpuscles of Meissner develop first in the periphery and then towards the centre of the skin area. In the newly developed papillae new corpuscles of Meissner were formed, and the curious pattern of the stratified wedge-shaped

cells is already visible when the papilla has reached less than half its normal height and before there is a trace of ingrowing nerve visible. The end-ramification

and end-nets of the innervating neurofibrillar strands become visible inside the stratified tactile cells when the papilla in which the tactile corpuscle is forming has reached about half-way up the epithelium. The developing tactile corpuscle itself always lies at the top, increases in height with, and remains at the top of, the growing papilla even when the papilla of connective tissue has reached its definitive height. The innervating neurofibrillar strands become richer and more complicated, and the extremely delicate strands which first appear grow thicker, exactly as happens in the development of the organ of Eimer in the snout of the mole, the details of which I have already described (see p. 15). Here, too, I am convinced a differentiation *in loco* of the neurofibrillae takes place, although this is very difficult to prove.

In Dr. van Straten's case the same procedure was followed. After the removal of the first piece of skin, about three months was allowed for healing to become complete before the regenerated piece was again removed. There is only this one case to record; an engineer was operated on in the same way, but refused to have the piece of skin removed for the second time, because he was afraid of infection during the healing process since his work involved daily contact with unclean machinery. The great advantage of the case of Dr. van Straten was that it was here possible to follow the healing process during all its phases, to take as many fingerprints as was considered advisable, and to study the process of healing physiologically as carefully as possible. This was done as before by Dr. Stenvers. The fingerprints showed the gradual formation of new ridges on the smooth new epidermis, the course of these ridges, the skin retraction, and the formation of new sweat glands, &c. The retraction of the skin seemed to be somewhat greater than in the



monkeys, but in the central portion of the regenerating skin the mode of formation of new ridges was exactly the same as in the *Macacus rhesus* (see Fig. 14, A and B).

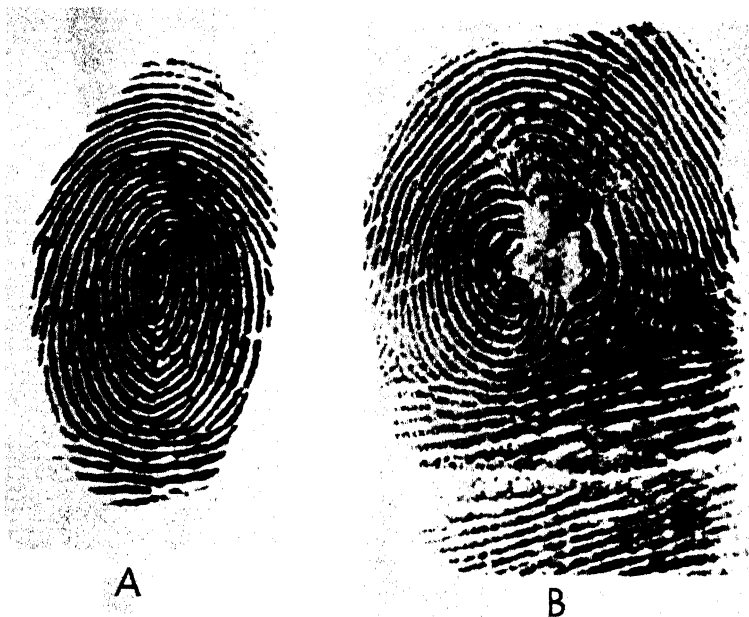


FIG. 14, A and B. Ridges of skin of human finger-tip. (A) Normal. (B) Regenerated after removal of the skin (9 weeks after the operation).

The study of the cross-sections showed us that inside the new papillae of the connective tissue, new corpuscles of Meissner were formed in exactly the same way as I have described above for the monkeys. Here in the human skin there seemed to be a greater number of intra-epithelial free nerve-endings present than in the fingertips of the monkey. But this may perhaps be ascribed to an incomplete impregnation in the monkey material. Jalowy describes an exuberance of free intra-epithelial nerve-endings in his regenerating material after nerve section only.

As already mentioned, the sensory innervation, pain spots, &c., were tested and mapped out very carefully by Dr. Stenvers. The enlarged map of his findings,



FIG. 15. Transverse section through regenerating corpuscle of Meissner in a pain spot of the regenerated piece of skin of Fig. 14B.

shown in a diapositif, corresponds exactly with the ridges of Fig. 14 B. Exactly the same protopathic sensibility as in the case of Dr. Heringa proved to be present, and the results of the study of the sections were exactly the same. There was no trace of developing sympathetic fibres or endings, but developing Meissner corpuscles (see Fig. 15) could be seen everywhere in the growing papillae. In the epithelium newly formed intra-epithelial nerve-fibres were visible.

Two distinct pain spots were exactly localized by

Dr. Stenvers. In one of these spots the sections showed a marked accumulation of two or three large corpuscles of Meissner (see Fig. 15); in the other only a large papilla was visible, containing curiously shaped inter-twinings of thick nerve-fibres without any distinct shape reminiscent of known forms of skin-endings.

Study of the sections has not yet finished, but these preliminary observations are sufficient to indicate the way in which such regeneration takes place, and the regular way in which healing takes place.

In this chapter an attempt has been made to show how the nervous elements innervating the skin and giving us a many-sided contact with the outer world behave under normal and abnormal conditions. Firstly after chemical stimulation and during regeneration. Secondly the method of regeneration which re-establishes an efficient sensory contact with the outer world after entire skin removal. All this shows the efficient way in which nature is able to re-establish an harmonious relationship between the organism and the surrounding world. It is primarily the nervous system which is necessary for the development of this harmonious equilibrium, and we see that it grows out, develops, and regenerates everywhere in the surrounding tissues, so that these are once again brought into relationship with the surrounding world.

In the following chapter the details will be given of the different sympathetic nervous elements innervating the skin and the other tissues of the body, and the problems surrounding these most complicated and important structures will be discussed. They are of quite a different nature from the problems outlined in this chapter, the difficulties are far greater as are the divergences of opinions and explanations given. The final solution is still far distant, the investigation therefore is even more fascinating.

## CHAPTER II

### THE SYMPATHETIC GROUND-PLEXUS IN THE GLANDS, MUSCLES, AND CONNECTIVE TISSUES OF THE BODY

AT the end of the first chapter the question was asked, in consequence of the discussion on the anatomical basis of Head's theory of protopathic sensibility, whether there were sympathetic fibres in the tissues of the skin or not. The answer is in the affirmative, for the skin and its derivatives are perhaps the most richly endowed with true sympathetic fibres of any tissues of the body. This is not devoid of meaning, for when studying the sympathetic plexus in different tissues one is astonished at its abundance and profuseness throughout the whole body.

This fact alone would be sufficient to excuse the devotion of a whole chapter to a discussion on this subject, but there is more to it than that. It is precisely here that nerve-fibres do not necessarily come into contact with definite end-organs of different and often very complicated structure. They are not adapted to convey a distinct and sharply defined impulse to or from end-organs, but often have to carry very subtle and indefinite general impulses to tissues which respond to these impulses in a slow way, in many cases in so slow and indefinite a way that it takes a series of very difficult and subtle physiological experiments to unravel it.

I need only to call your attention to the long series of physiological experiments on the actions of the sympathetic published by Asher, of Bern, and his many pupils (1935-7).

It is here that one may ask whether the strands of neurofibrillae, forming this plexus and coming into close contact with the elements of the tissues them-

selves, remain independent of each other or build up reticulated structures in which the independence of the different neurites is entirely lost and for which new methods of connexion with the surrounding tissue elements are needed to convey to them these indefinite general impulses which are of such great importance to the organism. In what way do these strands of sympathetic fibres influence the differentiation of the surrounding tissue and how do they act upon it?

Thus it will be clearly seen that the whole battle concerning the structure of the nervous system and the connexions of its elements with each other and with surrounding tissues has to be fought again over this peripheral system of nerve-fibres. For instance, it is just here that Ruffini denies even the existence of nerve-endings, and speaks of nerve expansions to illustrate his view that the nervous structure never ends freely but is everywhere continuous in a closed peripheral network (*circuito nervoso chiuso* of the Italian authors). And it is here, of course, that the outcome of the contest will be of fundamental importance in our general conception of the organism as a whole. It is here that the old conception of the independence of the cellular elements, the so-called mosaic theory of the organism, will be most severely put to the test by newly acquired facts. And this is even more the case when in the third chapter the so-called 'interstitial cells' will be seen coming into the foreground of the battle and playing their allotted part in the fray.

It is thus obvious that, in these two chapters especially, an impersonal neutral treatment of the subject cannot be expected. Personal convictions have to be brought to the fore and personal interpretations to the descriptions of the facts. An objective method of treatment will be attempted, but nevertheless personal opinions will come out and distinctly colour the whole

subject. This should not be objected to, for a purely neutral descriptive treatment of any subject is to be found in a book of abstracts and not in a series of lectures like these, a monograph in which the reader should expect a personal interpretation of the subject based upon personal research and criticism.

The problems to be discussed in the course of the following chapters are therefore concerned with the form and distribution of the sympathetic end-formation throughout the different parts of the body, and the ways in which this end-formation is connected with the surrounding elements and the manner in which the nervous stimulus is conducted to these surrounding elements.

Since one is writing in the language of the country which produced Langley, Sherrington, Adrian, and Dale, it would be a little presumptuous to discuss the physiological problems of the synaptic membrane of Sherrington, the humoral transfer of the stimulus, or the secretion of acetylcholine; in general the physiological synaptic problem. This contribution will be confined to the morphological side of the problem, and only where inevitable a few steps will be ventured on the less familiar ground of physiological theory, to discuss the probable physiological meaning of the histological details and their physiological implication.

It must never be forgotten that morphological details everywhere only derive their full value in view of the physiological and functional insight which they are able to furnish. Only when one is able to give a physiological interpretation of a given morphological detail, even if it is only in the form of a new demonstration of the harmony in nature and in the living individual organism, only then can one say that one understands it; that it has given us new insight into the ways of nature.

It is not necessary to emphasize here the importance of the sympathetic nervous system to the body. In it are incorporated all the so-called vegetative functions of our different organs, and its greatest value is in the curious antithesis in its functions; contraction and distension of the walls of the blood-vessels, assimilation and excretion, acceleration and retardation of the heart-beat, formation of different kinds of secretion products by the same gland, growth and reduction in size, all physiological differences incorporated in what we know as the sympathetic and the parasympathetic system (Langley).

It has a curious independency. As is well known, Cannon has reported experiments in which he removed as far as it was possible the entire sympathetic trunks of both sides from cats, dogs, and monkeys. The animals not only survived the operation, but when treated with care they lived as long as a healthy animal. The operation left the local visceral regulators deprived of all control from the central nervous system, for all pre-ganglionic fibres were cut and a large portion of the post-ganglionic fibres were removed. Nevertheless the animals remained alive when properly shielded from external disturbances, the remaining portion of the sympathetic nervous system being adequate to maintain vital functions under equable conditions.

On the other hand, as far back as the beginning of the nineteenth century, Larrey demonstrated that violent emotions of fear and mental anguish followed the irritation of the coeliac plexus. The influence on the character and psychical emotions of patients suffering from tumours of the pancreas which disturb the elements of the coeliac plexus is well known. It is also known that some of the peripheral sympathetic plexuses, such as the submucous and the myenteric plexuses of the small intestine, are capable of executing complete

reflexes quite independently of any extrinsic control (Cannon).

Impulses given by the sympathetic are as a rule of a general nature. Whereas ganglion cells of the higher

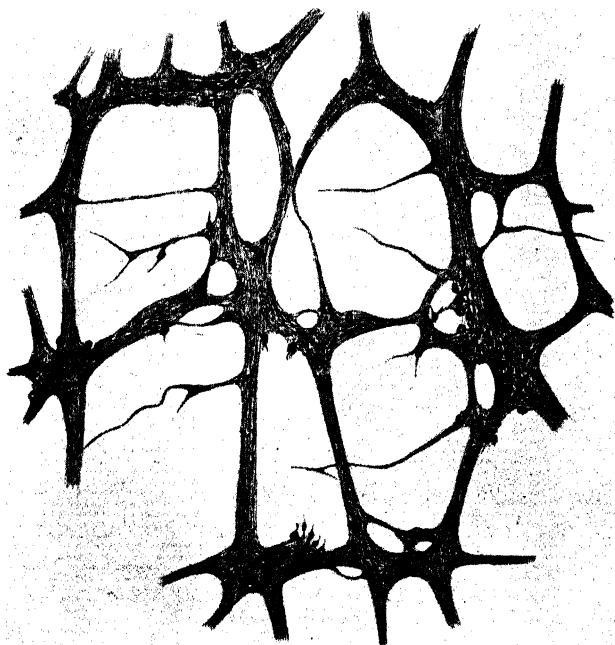


FIG. 16. General view of the plexus entericus in man.  
After Stoehr, 1933.

nervous centres are arranged in distinct patterns forming distinct architectonic groups, this grouping being most complex and most delicate in the highest cortical centres of the cerebrum, the ganglion cells of the sympathetic nervous system are scattered or lie in groups (Fig. 16) without definite arrangement, even in the larger ganglia such as the coeliac plexus, where there is a simple enclosure by a capsule of satellite cells. Most investigators are now of opinion that all the



sympathetic elements lying in these groups are of an efferent nature. Some admit the possibility of local visceral reflexes, such as peristalsis, being affected by axon reflexes within the neurones of these outlying sympathetic ganglia. In the third chapter these points will be discussed in more detail. Here it is only necessary to show the general importance and independent nature of the sympathetic system and the impulses travelling therein.

From these considerations it is clear that we have to study the sympathetic nervous system independently of the central nervous system, and that problems arising from its investigation are of a different nature from those elicited by a study of the central nervous system. The sympathetic nervous system thus requires separate methods of study.

As has been mentioned already, it will be in the end-formation of the sympathetic system that difficulties concerning the vagueness and the inadequacy of our previous conceptions will come to the fore. Especially with regard to the independence of the cellular units in the multicellular body, and of the independence of the neurones and the sharp line of demarcation between elements which conduct the nervous stimulus and those which transfer it to the innervated tissue elements. It is on these points that opinions are most divergent.

Three different theories concerning the sympathetic nervous end-formation are at present in the field and still being discussed.

Firstly the school of Cajal, adherents to the old, classical neurone theory, would solve the problem in the most simple way. They believe that sympathetic ganglion cells, whether they lie inside the spinal cord or are distributed in the sympathetic ganglia of the sympathetic trunk, or in peripheral ganglia, send their processes, the post-ganglionic fibres of Langley, the

*Nervenfasern zweiter Ordnung* of Kolliker, always as independent fibres, which remain independent even though they branch and twist profusely into very complicated plexuses. These fibres pass into different tissues, always remaining independent from each other until they reach their endings, which lie on smooth muscle cells, gland cells, &c., where they form delicate small end-rings or end-nets.

However, one must take into consideration the following facts: anastomoses between different nerve-fibres in the living growing body, as well as in cultures of the embryonic nervous tissues (Lawrentjew, Grigorieff, Levi, Mossa, Speidel) have been described most accurately in a number of cases, and undoubtedly present a feature of normal development. During the development of somatic motor nerves a syncytial stage appears between the outgrowing of the cell-processes of the motor ganglion cells and the formation of the definite motor end-plates on cross-striated muscle-fibres (Boeke). It then seems difficult to suppose that in the sympathetic end-formation with its extensive plexuses, and the general character of its impulses, this rather simple mode of nervous end-formations, consisting of independent nerve-fibres and independent small end-rings, should be the method followed. Even in a very primitive enteric plexus such as that in *Amphioxus lanceolatus* (Boeke), the anastomoses of different cell processes may be studied with the utmost clearness. Why should it be entirely absent in higher forms, where the co-operation between different nervous elements must be so very much more precise, and is also so much more complicated?

With regard to the second theory, some years ago Lawrentjew (1926) and van Esveld (1928) introduced a new element into the discussion, 'Interstitial cells'.

As is well known, Cajal described years ago *neurones*

*sympathiques interstitiels*; small triangular or spindle-shaped cells having cell processes which seemed to anastomose with each other, and which stained black in his Golgi preparations. These were found in the

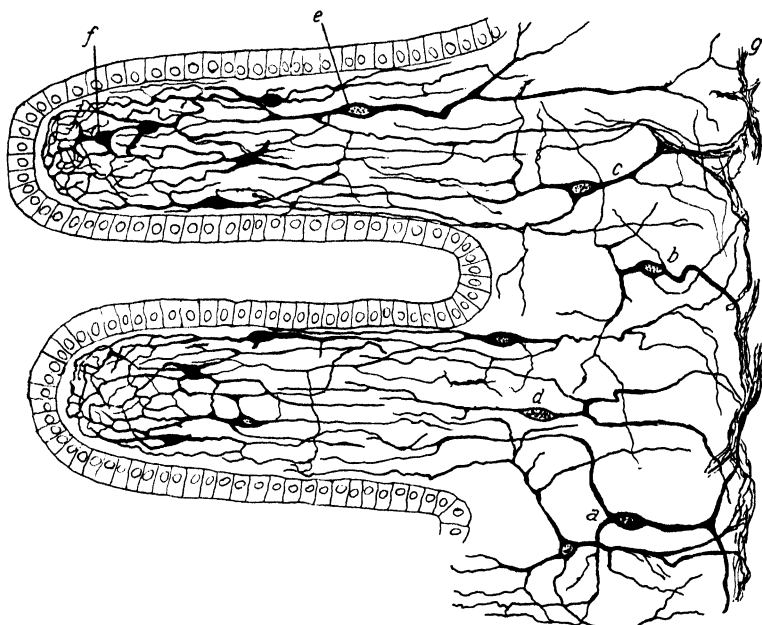


FIG. 17. Interstitial cells and plexus in the mucosa of the small intestine of a Cobaya. After Cajal, 1894.

sympathetic plexus in the wall of the stomach and intestine of frogs and different mammals. He adhered to his original description in his last publication in 1936. In 1926 Lawrentjew investigated these elements described by Cajal and gave them a central position in his description of the end-formation of the sympathetic nervous system. Cajal could not find any definite connexion between these cells and the elements of the plexus of Auerbach or Meissner, but supposed that they were under the influence of the real sympathetic ganglion cells. Lawrentjew followed up this suggestion

and found them to be always lying at the end of the neurofibrillar strands of the plexus and in this way forming an intermediate element between the strands, viz. the smooth muscle-cells.

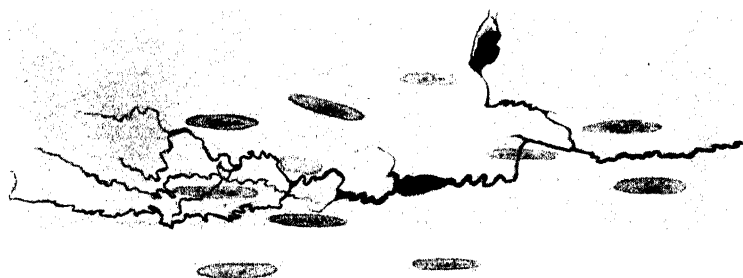


FIG. 18. Interstitial cells in plexus entericus of the cat in the smooth musculature. After Lawrentjew, 1926.

Van Esveld, who followed him, explained the results of his physiological experiments by the presence of these interstitial elements inside the muscle-tissues even when the true ganglion cells had been removed. According to both workers the interstitial elements were arranged syncytially and formed the end of the efferent sympathetic pathway, being connected with the protoplasm of the innervated elements by means of an intermediate network of protoplasmic origin, the 'periterminal network' described by Boeke and Heringa.

Following the original description by Cajal, an extensive literature has developed around these interstitial elements. Some have regarded them as connective tissue elements, others have proclaimed their nervous nature. In my opinion, they are of the utmost importance in our conception of the efferent sympathetic pathway; but as the third chapter will be devoted to a discussion of these elements and their probable place

and function in the efferent sympathetic pathway, we will leave them for the moment and return to the subject later.

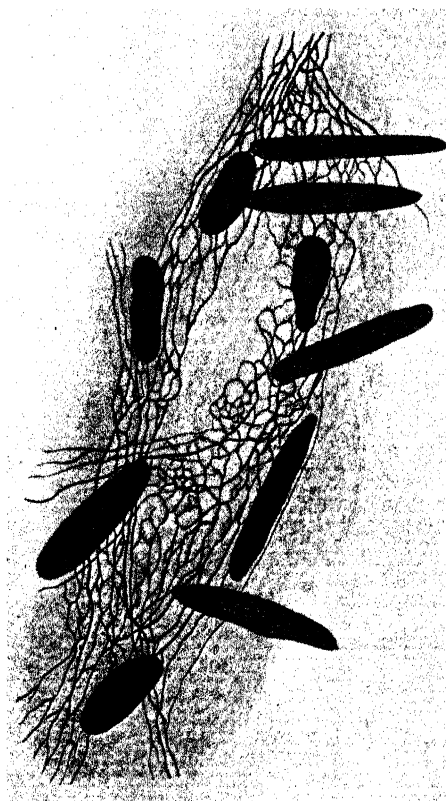


FIG. 19. Terminal reticulum in plexus entericus of man. After Stoehr, 1933. With oval nuclei of Schwann and elongated nuclei of smooth muscle.

The third theory is diametrically opposed to both the views described above. It is the conception of the 'Terminal reticulum' of Stoehr, Reiser, and Sunder-Plasmann (1932-7). Compare Fig. 19 and Fig. 20.

According to Stoehr and Reiser, sympathetic ganglion cells are not to be regarded as separate individuals, whose cell processes end either freely or in connexion

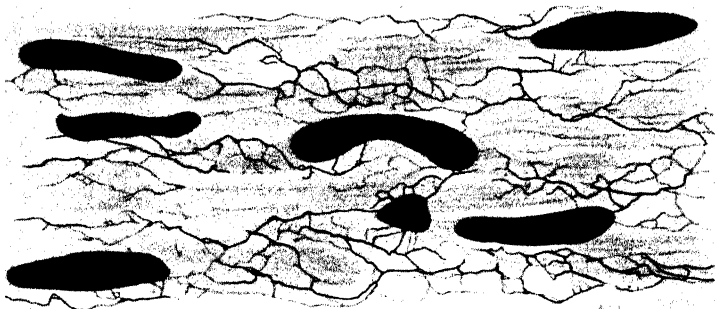


FIG. 20. Terminal reticulum in appendix of man. After Reiser, 1933.

with neighbouring tissues by means of true nervous synapses; but as forming large syncytial masses the processes of which anastomose everywhere and form an inextricable mass throughout the whole body. The nerve processes of the sympathetic ganglion cells merge into an exceedingly fine and delicate network, mostly of an alveolar nature. This proceeds to form a kind of intermediate protoplasmic substance, which surrounds every cell or muscle-fibre in the body as a very delicate veil, passing into continuity with the protoplasm of the elements themselves.

There are no true nerve-endings to be found. This formation is present in the periphery as well as in the end-formation of the intestinal plexuses, in fact everywhere in the body where sympathetic elements are found. There are no nerve-endings at all, not even sharply defined endings of the argentophile neurofibrillar structure can be seen. The endings which have been described by various authors are considered by Stoehr and Reiser to be artefacts, caused by an

insufficient impregnation of the argentophile substance. Everywhere in the sympathetic system the nervous substance passes into a very delicate alveolar structure, a sort of intermediate substance between the nervous strands and the protoplasm of the innervated elements.

To quote Reiser, who seems to be the original author of this conception: 'das Terminalreticulum ist wahrscheinlich als ein Zwischengewebe anzusehen, das gleichzeitig die Elemente des Nervensystems und die des innervierten Gewebes in kontinuierlich fließenden Zusammenhang bringt, so daß ein scharf abgrenzbares Ende der nervösen Substanz nicht zu erkennen ist' (Reiser, 1933, p. 637). According to Stoehr, the neurofibrillar structure in the end-formation of the sympathetic plexuses forms at its terminals delicate anastomosing strands of a more protoplasmic nature, the 'Plasmastränge', which pass into the terminal reticulum mentioned above. This particular structure 'breitet sich im Bindegewebe überall so aus, daß man den Eindruck gewinnt, als sei das nervöse Terminalreticulum mit seinen Waben so gesponnen, daß jede Zelle von seinen Fäden zunächst einmal wie mit einem zarten Schleier umhüllt wird' (Stoehr, 1932, p. 427). He goes on to say: 'man gewinnt stellenweise den Eindruck, als würden die Maschen des Reticulums nach der äußersten Peripherie immer zarter and blasser, vielleicht weil sich in ihren Einzelementen nervöse Substanz nicht mehr in genügender Menge vorfindet, um noch einen Niederschlag des Silbers hervorzurufen. Somit besteht möglicher Weise Grund zur Annahme, daß sich das nervöse Terminalreticulum allmählich und kontinuierlich in ein immer feiner werdendes, wabiges Protoplasma von vielleicht nicht mehr ganz spezifisch nervösem Character fortsetzt. Dann hat man aber schon das periterminale Netzwerk vor sich.' I have

quoted Stoehr at length because in their later writings these authors often confuse the terminal reticulum and the periterminal network, and again, the sympathetic ground plexus, which will be described more fully in the following pages, is often confused with the terminal reticulum. In his last paper, however, Reiser (1936) admits that these two structures are fundamentally different ('zwei verschiedene, eigentlich unvergleichbare Dinge'. 'Terminalreticulum und sympathischer Grundplexus sind demnach morphologisch grundverschiedene Nervenformationen.' Reiser, l.c., p. 268).

Thus, we see that the conception of the terminal reticulum has greatly altered during the last four years. The above-named authors in their first publications described their terminal reticulum as a non-nucleated structure, comparable to the hypothetical ground-net described by Held in the central nervous system, but in their later writings they described scattered nuclei of Schwann lying in their terminal reticulum, making the whole conception even more difficult to understand.

Reiser in his most recent paper mentioned above again compared his terminal reticulum with the periterminal network in which nuclei are conspicuously absent, since it is nothing but a protoplasmic intermediate substance, lying within the protoplasm of the innervated elements themselves. Thus the whole conception is still somewhat confused.

When one examines Stoehr and Reiser's pictures it is often difficult to consider it as a nervous structure at all; it often looks more like a mesh of connective tissue-fibres (Boeke, 1933, p. 252) than like a nervous structure (see Fig. 20). The cardinal point of the whole conception, however, is that there are no neurofibrillar endings present in the sympathetic end-formation, and



that there is merely a gradual transition from a neuro-fibrillar network into a very delicate network of a more protoplasmic nature, which is present everywhere in the body. Into this network pass nerves which contribute to the sympathetic system in its broadest sense, for instance both vagus and sympathetic nerves, and according to Reiser even afferent and efferent nerves. To quote Stoehr, 1933, once more: 'wir sind dazu übergegangen, eine freie, plattchenartige Endigung der vegetativen Nervenfasern auf oder innerhalb der glatten Muskelfaser und an der Gefäßwandstelle abzulehnen und statt dessen den Begriff des nervösen Terminalreticulums aufzustellen, analog dem des Held'schen Grundnetzes' (l.c., p. 151).

As soon as the first papers by Stoehr on the terminal reticulum appeared I repeatedly called attention to the danger of mistaking reticular fibres of connective tissue origin with nervous structures. In his later writings Stoehr himself acknowledges that when using silver methods in the study of nervous end-formations, one has always to be very careful not to confuse connective tissue fibres with delicate fibres and meshworks of nervous origin; 'man muß immer bedenken, daß es bei Anwendung der Silbermethoden sehr leicht zu Verwechslungen von Elementen des Terminalreticulums mit solchen des interstitiellen Bindegewebes kommen kann.' (Stoehr, 1934.)

This danger has to be kept in mind when studying silver preparations, in which argentophile fibres of connective tissue origin may become impregnated together with nerve fibrillae. All histologists have to avoid this error, and only long years of practice can enable one to avoid it in every case. This is especially true in the study of nerve end-formations where exceedingly delicate nerve end-fibres are losing the chemical qualities which enable them to be stained

selectively, so that we can distinguish their character in our preparations. Even in the most carefully made preparations such confusion may arise. This is shown in the differences of opinion between Dogiel and Cajal concerning the nature of the interstitial cells.

It is just this difficulty which has made the whole problem of the terminal reticulum even more confused. An American histologist, Nonidez (1937), tried to demonstrate that the networks described by Stoehr and his followers are nothing but connective tissue networks of the nature of reticular fibres having nothing to do with nervous structures. We will have to refer to these objections later on (see p. 80).

Thus one can see that there is no unanimity of opinion whatever concerning the problem of the end-formation of the sympathetic nervous system. The problem is one of fundamental importance in regard to the conception of the functions of this part of the nervous system, and will have to be worked out afresh. Is the end-formation of the sympathetic system a reticular nervous formation or not? Is it solely of an efferent nature, or are afferent fibres mixed up in it? Is it richly developed or not? Is it possible to distinguish it from other structures? In what manner is it connected with the other elements of the body which are innervated by it? What is its function? Each question forms a problem in itself. And yet, as Pierre Marie once said: '*le grand sympathique, malgré les nombreux et importants travaux qu'il a suscités, n'en reste pas moins la Terre Inconnue, peut-être la Terre Promise, après la conquête de laquelle soupirent Anatomistes, Physiologistes et Cliniciens.*' The sympathetic nervous system is still unknown territory, and as its importance in the organization of our entire body is acknowledged more fully every day, it would appear to be the Promised Land, which every histologist,

physiologist, pathologist, and clinician hopes and tries to conquer.

It goes without saying that in a brief monograph such as this, it is quite impossible to answer all the questions formulated. All one can do is to try to give a general idea of the end-formation of the sympathetic system, and the best and easiest way to arrive at that will be to give a short historical outline of the manner in which the conception of a dense, reticular, sympathetic ground-plexus was arrived at, and of the difficulties which had to be surmounted.

In mammals the foremost part of the tongue is innervated only by the lingual and hypoglossal. The glosso-pharyngeal nerve only supplies the posterior part of the tongue. Thus when these nerves are cut and time given to allow the sectioned nerves to degenerate, all the somatic nerves disappear, and in cross-sections through the tip of the tongue the only nerves found on the side where the nerves were severed must be of a *sympathetic* nature, the post-ganglionic fibres of the ganglion cells scattered throughout the tongue. Thus in a hedgehog on the left side both the lingual and hypoglossal nerves were cut. Two months were allowed for degeneration of the fibres severed from their point of origin, and in order to be sure that no regenerating nerve-fibres would spoil the picture, after this lapse of two months the scar was re-opened and both nerve-trunks were again severed. After two weeks the animal was killed, the blood-vessels were first washed out with Ringer's solution and then injected with formol solution.

In cross-sections through the foremost part of the tongue the nerves on the right side of the section were found to be intact. On the left side every somatic nerve-fibre had degenerated. In the papillae of the mucous membrane there appeared a rather dense

plexus of very delicate amyelinated nerve-strands surrounding the blood capillaries, which followed the basal line of the epithelium, and wound its way to-

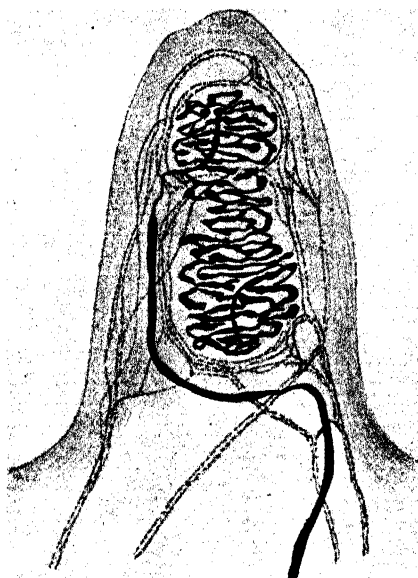


FIG. 21. Corpuscle of Meissner with pericorpuscular nerve-plexus. After Crevatin, 1899.  
Human skin.

wards the apices of the papillae, and which was connected with nervous strands in the connective tissue underlining the epithelium (Fig. 23). In the normal half of the tongue it was also present, but here was mixed with sensory nerve-fibres so that it was impossible to separate the two systems. But in the left half of the tongue, this plexus was the only nervous structure left. Thus it must be of a sympathetic nature.

This sympathetic plexus is rather dense. It reminds one strongly of the pictures of perivascular and pericorpuscular nervous plexus in the skin and the mucous membrane of the mouth (Fig. 21 and Fig. 22) given

by Italian histologists of the Golgi school in the beginning of this century (Ruffini, Cecherelli, Sala, Crevatin). These authors worked with gold chloride,



FIG. 22. Perivascular nerve-plexus of sympathetic nerve-fibres in human skin. After Crevatin, 1900.

which is not always sufficiently selective for nervous strands to allow of unchallengeable conclusions, and their observations have fallen into oblivion. However, in my opinion, they were perfectly right, the dense nerve plexus of sympathetic nature which they saw in their preparations is real, and its sympathetic nature proved by the degeneration experiments. Its connexion with nervous strands in the submucous tissue is undeniable. The details of this plexus, its richness and its connexions with the epithelium, with taste buds, and with the underlying connective tissue, can be studied in thin sections with the utmost clarity. However, since this monograph can deal only with the broad outlines of the sympathetic plexus, we will leave this point and pass on to another field of investigation.

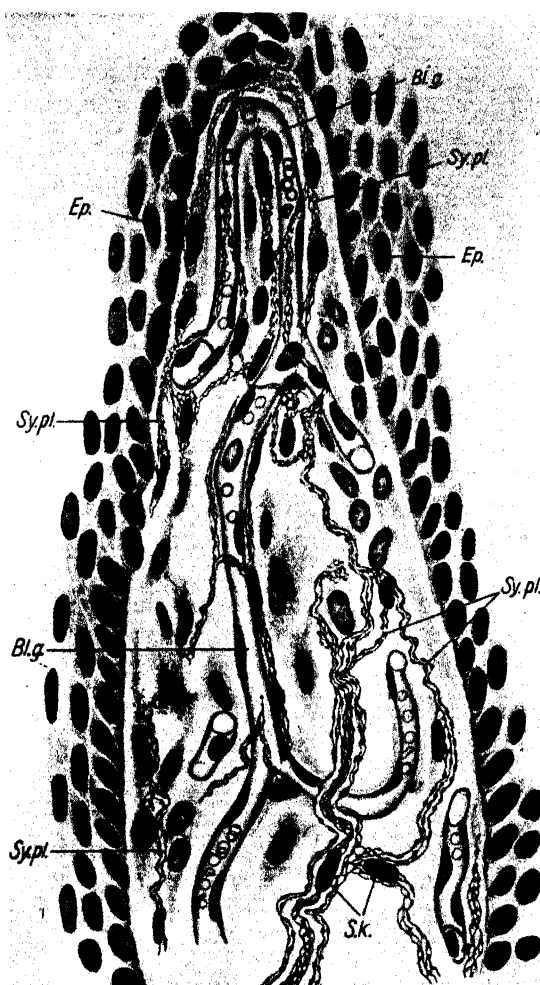


FIG. 23. Sympathetic nerve-plexus in a papilla of the mucous membrane of the tongue of a hedgehog, after section of the cerebral nerves, operated half of the tongue.

After Boeke, 1933.

In a mucous membrane, or in the skin, in fact in most tissues of the body, a plexus of this nature extends in three dimensions. For this reason, in a thin section the

connexions of the nerve-fibres are mostly severed. We cannot determine whether it is a network or simply a dense plexus of interwoven separate nerve-strands.

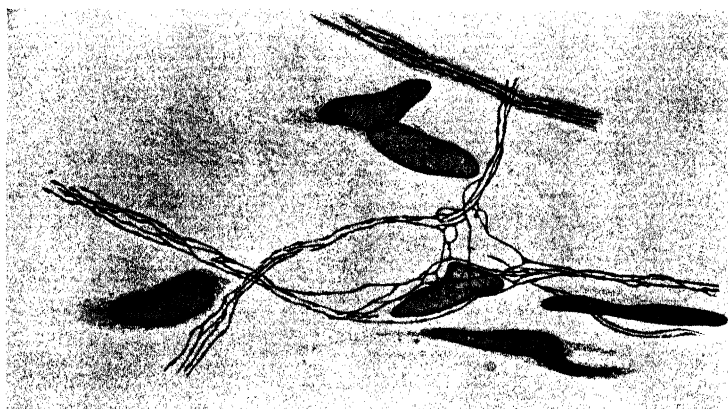


FIG. 24. Nervous plexus in the loose connective tissue of the chorioid coat of the human eye. After Boeke, 1933.

In the thin coats covering the eye-ball, however, the sclerotic, the vascular coat and the tissue between, we find tissues exceptionally well adapted to this purpose. In these thin layers the nerve-strands extend practically in one plane, and even in very thin tangential sections through these coats the most delicate neurofibrillar strands may be followed with the utmost exactness for a long distance. Here the problem had a chance of solution. In thin tangential sections from Bielschowsky preparations of the human eye-ball there appeared a beautifully impregnated plexus of the most delicate varicose nerve-fibres, which could be studied with the utmost exactness (see Figs. 24 and 25).

In the connective tissues of the choroidea and accompanying the blood-vessels a plexus of very fine, delicate, non-myelinated nerve-fibres was found everywhere running in small bundles containing intercalated

nuclei, exactly like the 'cable system' of the terminal elements described by Lawrentjew. He described some of the nuclei as 'interstitial cells'. This question will

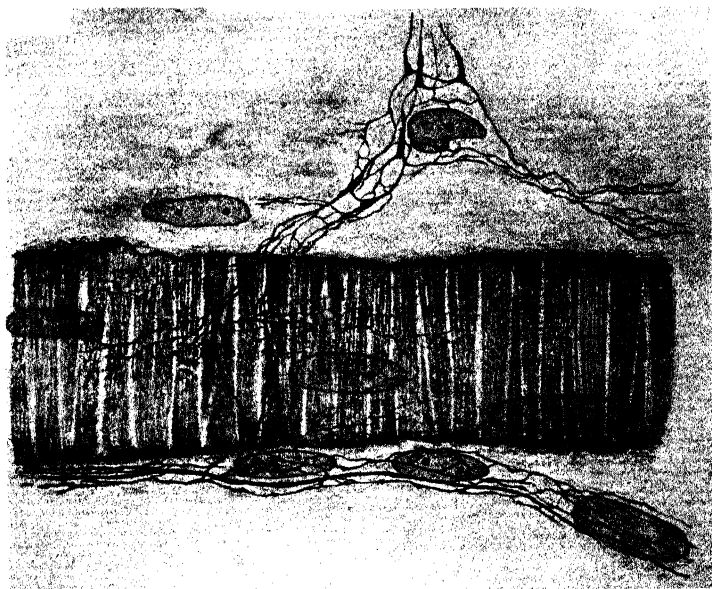


FIG. 25. Blood-vessel in the chorioid coat of the human eye, with nervous plexus. After Boeke, 1933.

be dealt with more fully in the third chapter. This system is similar to what Stoehr called the nervous plasmodium and what Reiser in his latest paper (1937) thought fit to baptize with a new name, the 'prae-terminal network'.

They are seen running everywhere throughout the connective tissue of the choroidea and between it and the denser sclerotic coat. These bundles consist of very delicate varicose nerve-fibres and have such a peculiar appearance that they can be distinguished with the greatest certainty in every case from connective tissues surrounding them. They spring from the thicker



nerve-bundles, to which they could always be traced. They do, however, follow an independent course through the connective tissue. The varicose nerve-fibres continuously anastomose with each other. Of course such an anastomosis may be due to fixation by a formalin solution, which, as is known, is prone to cause an adherence of very fine neurofibrillae, when they run inside the same protoplasm syncytially. Here, however, the strands are often so loosely built, and the thin neurofibrillae run so far apart from each other although within the same protoplasmic formation, that an artificial adherence between them seems to be out of the question. The anastomoses visible (Fig. 24) must have been present in the living tissue. These loose strands of neurofibrillae are seen following the blood-vessels everywhere (Fig. 25). They run so close to the endothelium as sometimes to appear to be embedded in it; indeed, the neurofibrillae often lie in the same plane as the nuclei of the endothelial cells. Even capillaries are encircled by them. Besides these vascular bundles, we see similar strands running everywhere in the connective tissue. In the coats of the human eye it is very easy to trace them to their origin from thicker nerve-bundles, so that their nervous nature cannot be doubted. In their general behaviour they look exactly like the pictures of perivascular plexuses given by Crevatin, Sala, and Ceccherelli, mentioned above. We may safely conclude that we have here the selfsame nerve plexus of sympathetic origin, which was found in the connective tissue of the mucous membrane of the mouth after sectioning of the somatic nerves. It is in the nature of a real network, the different neurofibrillar threads anastomosing freely with each other and lying embedded in the same protoplasmic covering.

As mentioned already, this sympathetic nerve plexus is found not only in the connective tissue of the eye-

coats, but also covering the walls of the small arteries and capillaries. It seems to be of general occurrence. It was found, for example, in the walls of arteries of all sizes, small, medium, and large; in glands, the parotid and lachrymal; in the human skin and orbit and tongue of the hedgehog, cat, and rabbit, as an intricate network of delicate varicose neurofibrillae.

Although much finer and more delicate, it might be compared with the network described by Stoehr and by Leontowitsch as the second network in the arterial wall, and with the nervous plexus in the intestinal wall, described so well by Catherine Hill from her wonderful methylene blue preparations. It appears even here not only as a plexus with neurofibrillar strands crossing and recrossing each other, but as a regular network of extremely delicate neurofibrillae with intercalated nuclei, precisely as I described it in the coats of the eye-ball.

In small arteries with only one layer of muscle-cells, it appears in the form of loose wavy threads of neurofibrillae with scattered nuclei. In the larger arteries with a muscular coat composed of several layers of muscle-cells it is found to spread out as a flattened plexus or network with wide meshes, composed of innumerable neurofibrillae crossing and anastomosing with each other in the most complicated manner. Dispersed nuclei lie between the neurofibrillae without the faintest trace of boundaries between them, exactly as in the nervous plasmodium described by Lawrentjew in the wall of the intestine.

Here, also, Lawrentjew described a real syncytial arrangement of the protoplasm of what are commonly called the sheath cells, or lemnoblasts, with the neurofibrillae embedded in it. There was no trace of a boundary between neurofibrillae and lemnoblastic protoplasm. Thus, according to his views, the distinction

between the sheath elements and the conducting protoplasm with its differentiation of the neurofibrillae is lost at this point just as he described happened in his system of 'interstitial cells', the details of which I hope to describe in my third chapter.

Figures only give an inadequate picture of the wonderful fineness and exuberance of this plexus, which covers the entire muscular coat and even extends between the muscular layers. In cross-sections or in consecutive longitudinal sections, it can be followed between the outer muscle-cells. Whether it is still present between the inner muscle-cells is difficult to determine, because it becomes so fine. It is more in the nature of the periterminal network which extends from the sharply impregnated neurofibrillar structures of the motor end-plates or the tactile corpuscles into the protoplasm of the sole plate of the muscle-fibre or into the protoplasm of the tactile cells.

It is found everywhere, and in favourable places in the impregnated preparations its connexion with the sympathetic ganglia is easily seen, as for instance in the musculature of the tongue, where sympathetic ganglia are scattered throughout the interstices of the muscle-bundles and therefore often lie in the neighbourhood of the blood-vessels studied. It has nothing to do with the argentophile reticular fibres of connective tissue origin as claimed by Nonidez (1937). Reticular fibres are often found in the preparations, but their form and arrangement are totally different. The connexion of the strands of the nerve plexus just described with true ganglion cells and with thicker nerve-bundles, which may be determined as undoubtedly of nervous nature, proves without doubt that they are of nervous origin. Moreover, they have exactly the same appearance as the vascular nerves described by Kolliker years ago in Golgi-preparations and by Dogiel in his methylene blue

preparations. Thus their nervous nature seems to me to be beyond doubt, as will be demonstrated again when discussing the relation of this plexus to the fat cells.

When studied under the best conditions of illumination and with the shortest focal length objectives and the highest resolution obtainable, it seems as if this plexus of delicate neurofibrillae extends to the muscle-cells of the tunica media of the vessels and continues into an extremely delicate network inside the muscle-cells. It there becomes lost in the fine longitudinal striation of the contractile fibrillae. That is to say, it seems to continue into a protoplasmic network visible as a very delicate rather granular sarcoplasmic alveolar structure which appears in well-impregnated fixed tissue elements; the so-called periterminal network.

In fixed and impregnated elements it is clearly visible, but one must never forget that in histology we are dealing with living elements, destroyed by the chemical action of fixatives and strong impregnating fluids. One is only studying the remnants of a living tissue put to death, and that what one sees of a protoplasmic network may only be of importance because it demonstrates that a protoplasmic connexion exists; a connexion between the living substance of the muscle-cells and the innervating elements, the neurofibrillar structures.

It is sufficient to draw the conclusion that the network which has been described here, and which may be compared with the dense network described by the authors mentioned above, is the real efferent innervation of the smooth muscle-cells of the blood-vessel wall covering the entire contractile coat and including all its elements. The nuclei dispersed throughout this syncytial nervous plasmodium are in the nature of interstitial nuclei.

In the tongue, the whole plexus with the nuclei

persists after sectioning of the lingual nerve. The fact that the nuclei with a little surrounding protoplasm remain as separate stellate cells after periarterial sympathectomy was described by Woollard (1926) in the intramuscular plexus which he observed in the wall of the sciatic artery. This may have been due to the method used. Methylene blue is often known to stain protoplasmic structures without staining the fibrillae connecting them.

This plexus is not only confined to arteries and veins. The same plexiform anastomosing bands of extremely delicate neurofibrillar strands are seen running alongside the capillaries, closely adhering to the endothelial wall, just as was pictured by Lawrentjew in 1926, and here, too, one may be certain of their nervous nature, for exactly the same picture of the capillary wall can be got by using methylene blue. This was shown by Lawrentjew in 1936 and by Kolossow in the same year. They have nothing to do with reticular fibres, as maintained by Nonidez, although these may sometimes present somewhat similar features. In a section in which both structures are stained, it is always easy to distinguish one from the other.

This plexus may be traced throughout the connective tissues exactly as the perivascular plexus of Crevatin and Ceccherelli, mentioned above. Strands of neurofibrillae can also be seen encircling and developing striated muscle-fibres, and are so closely applied to them as often to appear embedded in the sarcolemma, although they are always epilemmal in position. When studied under the highest powers of the microscope they are often found to be lying exactly in the same plane as the striations of the muscle-fibres. They are, however, often difficult to find because of the dark staining muscle-fibres themselves which render them invisible. One could observe them on the same muscle-

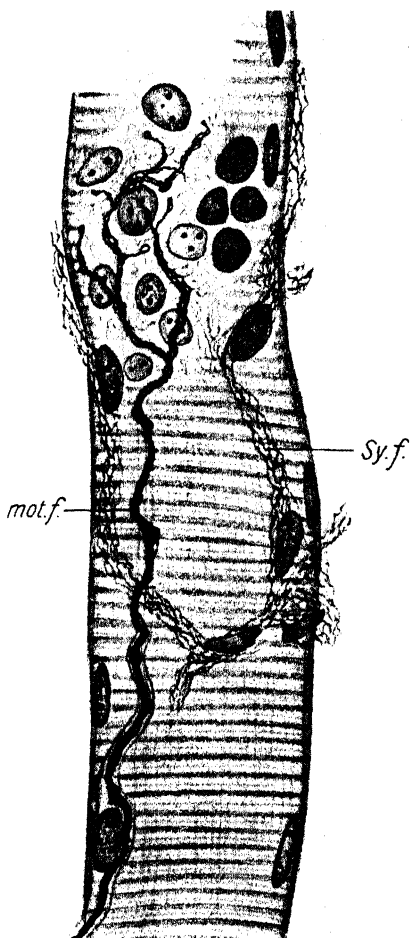


FIG. 26. Sympathetic and cerebrospinal motor-nerves on a striated muscle-fibre in the tongue of the hedgehog. After Boeke, 1934.

fibres as darkly stained motor end-plates (Fig. 26) and apparently in direct connexion with the protoplasm of the sole-plate.

When the motor-fibres degenerate after cutting of the efferent nerve, these strands remain intact as is

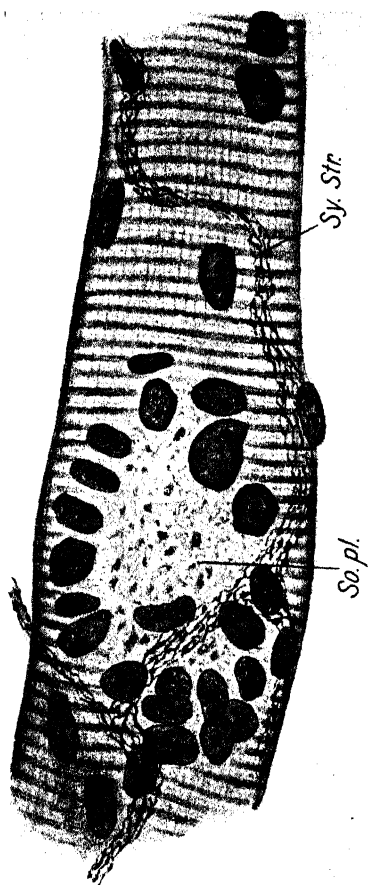


FIG. 27. The same as Fig. 26, after the section of the motor-nerve and subsequent degeneration of the somatic nerve-fibres. *So. pl.* = sole plate of the degenerated motor-nerve; *Sy. Str.* = intact sympathetic ground-plexus.

shown in Fig. 27. They appear to be in direct continuity with the plexus covering the walls of the blood-vessels. This may be of importance in the physiological connexion between the two in muscular contraction.

In the parotid and lachrymal glands of man and animals, for instance, this plexus is seen to present precisely the same features. We find the same dense and extremely delicate nervous network encircling and covering the clumps of gland-cells, and from this network spring the fine nerve-fibres which run between and enter the gland-cells.<sup>1</sup> As is well known, the masters of the methylene blue technique, Arnstein and Dogiel, described in various glands, especially in the salivary glands, two different sorts of nerve-fibres. The first, which forms the hypolemmal plexus of Arnstein, consists of fibres which do not enter into the gland-cell formation itself, but remain outside the basement membrane, and the second sort, forming the epilemmal nerve-plexus, consists of fibres which enter the gland tubules and run between the gland-cells. According to Dogiel these fibres often form a sub-epithelial plexus before they push their way between the gland-cells themselves to form the inter-epithelial plexus. These different nerve-plexuses and nerve-fibres were held to be responsible for the two different kinds of secretory products, produced by the same gland after stimulation of different nerves.

These various plexuses and nerves were found in the author's preparations exactly as described by Dogiel and Arnstein, but even the most careful study under the highest powers of the microscope, using the most powerful illumination, did not reveal any independence of the different structures. Both the fibres forming the sub-epithelial and the inter-epithelial nerve-plexus spring from the same ground-plexus encircling the clumps of gland-cells, outside the basement membrane.

<sup>1</sup> According to Jalowy even the strands of the sympathetic plexus themselves often lie embedded in the protoplasm of the gland-cells, and not beneath the cells outside their basement membranes (Jalowy, 1938).



We do not know as yet whether different and independent fibres run in the ground-plexus; certainly netlike anastomoses of its nerve-fibres are to be found everywhere.

After all, what is known about the pathway of a distinct nervous impulse within a neurofibrillar network or in a plexus, and what is known concerning the inhibitory or the accelerating nervous impulses in a plexiform or netlike end-formation? What do we know about the local degeneration and regeneration in such a nervous formation?

Perhaps the resonance principle of Paul Weiss, formulated in relation to the selective action of muscles and groups of muscles acting together may provide a solution here also, but at the moment we cannot say, and it would seem a little dangerous to denounce exact histological statements on the ground that they do not fit in with current physiological opinions and explanations.

As an histologist one can only say that both hypolemmal and epilemmal nerve-fibres can be seen springing from the same ground-plexus in which the neurofibrillae seem to anastomose freely with each other. The derivation of the intra-epithelial fibrillae, which are undoubtedly of nervous origin, from the ground-plexus is another proof of the nervous nature of this plexus, and it is this which is so important to establish with the greatest possible exactness.

In the fourth place, this network could be followed to the smooth muscle-cells of the arrectores pilorum, and in some places it could even be seen between the elements of the bundles of contractile fibres forming the smooth muscles of the dermal spines in the hedgehog. This is of interest because the action of these muscles is generally supposed to be voluntary in nature and therefore under the control of somatic nerve-fibres.

Thus it seems that one is entitled to sum up these observations in the following way. There exists a system of very delicate interwoven and anastomosing non-myelinated nerve-fibres, running in strands or flattened bands of extremely delicate neurofibrillae with scattered nuclei, forming the terminations of the sympathetic plexus, a part having been described as 'interstitial cells'. It is found in abundance in the outer layers of the muscular coats of blood-vessels, both in small and large vessels and on the walls of capillaries. In the tunica media of the blood-vessels it stands in close connexion with the muscle-fibres. As far as could be seen, it is found everywhere in the smooth muscle-tissues, in glands where fine fibres spring from it which run between and into the gland-cells, and in the connective tissues it may be compared with the perivascular plexus of Crevatin, and with the connective tissue nerve network of Leontowitsch. It runs around and between striated muscle-fibres, and in several instances bands of extremely delicate neurofibrillae could be traced to a sympathetic ganglion. No trace of cell boundaries or sheaths was to be seen in the strands; only intercalated nuclei. It represents a true nervous terminal plasmodium as formulated by Nageotte. In my opinion, this is the real efferent sympathetic terminal system. The neurofibrillae described by different authors in the adventitia of the blood-vessels and encircling the capillaries at some distance from the endothelial wall are apparently of an afferent nature and have nothing to do with this sympathetic plexus.

Before finishing this description two other examples must be referred to which are of interest in connexion with the relations of this plexus to different tissues in our body.

The first concerns glands which possess contractile elements surrounding the tubules, for example the

longitudinally or obliquely disposed contractile fibres between the epithelium and the basement membrane of the sweat-glands, or the peculiar flattened branched cells on the inner surface of the basement-membrane of the salivary glands. In both cases the contractile elements are in close connexion with the ground-plexus, each contractile element receiving a branch from it, which is thus shown once more to be efferent in nature.

The second example raises the problem as to whether there is a nervous connexion between sebaceous glands and the sympathetic system. Observations on the innervation of these glands are very scarce. Pensa (1897) described in Golgi-preparations a number of very thin fibres surrounding the glands; Kolliker and others could not confirm his statements. Kadanoff (1924) saw nerve-fibres in the connective tissue surrounding the glands, but could not make certain whether they belonged to the glands or the hairs. Stoehr (1932) was very sceptical of the existence of such nerves. Physiologically nothing definite is known. Schur and Goldfarb (1927) describe the curious uniformity and consistency of the fatty condition of the skin in healthy, normal individuals, from whose skin the fat has been removed by the application of fat-dissolving solutions of ether.

When the fat is taken away the normal condition is restored within ten to fifteen minutes. No further fat is then produced. In pathological cases the influence of the sympathetic nervous system on the secretion of the sebaceous glands seems to be beyond question. Marshalko (1905), Laignel-Lavastine (1924), Lhermitte (1922), and Cornil (1922) describe cases of unilateral hypersecretion of sebaceous fat (*visage huileux unilatéral*). Hypersecretion in tissues surrounding healed defects in the skin, and hypersecretion in a definite area

of skin, all point towards the distinct influence of the sympathetic nervous system upon the secretion of the sebaceous glands.



FIG. 28. Sebaceous gland in a transverse section through human skin of the cheek, with hair-root (*H.W.*) and gland cells (*Dr.*) with innervating plexus (*X*). After Boeke, 1934.

Because of the holocrine nature of these glands, individual innervation of the cells is not probable, the cells themselves being destroyed when the gland secretes. They are subsequently replaced by new secreting cells. However, in the figures from Bielschowsky—preparations of the human skin, there were found a great number of very fine varicose nerve-fibres surrounding the glands and forming a rather dense surface plexus. These fibres were invariably connected with the sympathetic plexus surrounding the hair roots and lying in the connective tissue surrounding them. There was no trace of nerve-endings, the flattened strands of neurofibrillae simply lay closely adherent to

the gland-cells. They never entered the gland, so far as I could see (Fig. 28).

From sebaceous glands to the fat-cells of the con-

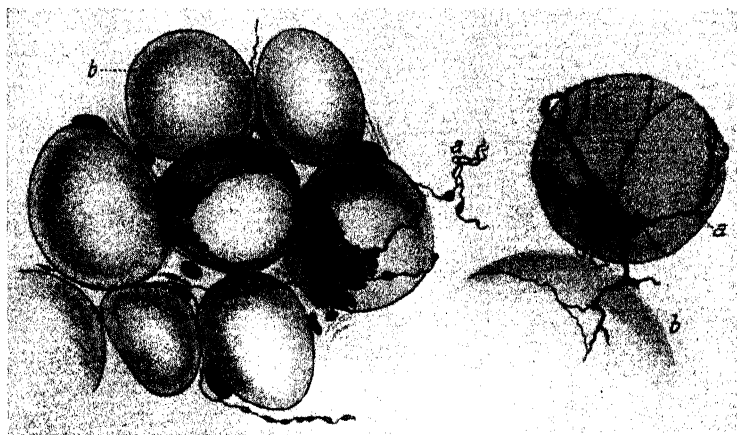


FIG. 29. Fat-cells with nerve-fibres, stained with methylene blue. After Dogiel, 1898. To the right an 'interstitial cell'.

nective tissue seems only a step *il n'y a qu'un pas*. And yet the conditions are totally different, for here can be seen connective tissue elements in which fat is permanently or temporarily stored. The fat may be lost or recovered again. The same cell may contain a large drop of fat, lose it, and under favourable conditions a new drop of fat may appear within its cytoplasm. In recent years renewed studies on basal metabolism have pointed definitely towards the existence of a direct influence of the sympathetic efferent nervous system upon the production and storage of fat in common adipose tissue. Direct experimental, as well as clinical, observations have been published in recent years concerning the influence of the sympathetic system on fat storage by a number of authors (see extensive literature cited by L. R. Mueller, 1931, and Hausberger, 1937). However, concerning the innervation of the fat-cells

nothing definite was known. Dogiel, the master of the methylene-blue technique, has shown two pictures of nerve-fibres surrounding fat-cells (Fig. 29). He thought

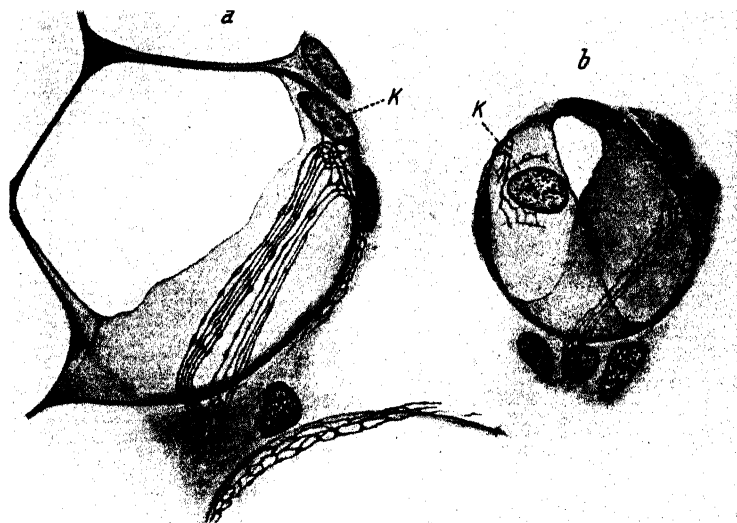


FIG. 30. Fat-cells of human skin with sympathetic nerve-fibres of the ground-plexus surrounding the cells, stained with Bielschowsky-method. After Boeke, 1933. *a* = extended fat-cell, *b* = less extended, nerve fibrillae not stretched; *K* = nucleus of fat-cell.

them to be sensory in character, although he pictures an unmistakable sympathetic cell (even an 'interstitial cell') lying close to the fat-cell (Fig. 29, towards the right-hand side). When one studies well-impregnated sections through a tissue containing numerous fat-cells such as the subcutaneous tissue of the human skin, the human parotid or lachrymal glands, &c., one finds such a close connexion between the sympathetic plexus and the fat-cells, flattened bands of delicate parallel varicose neurofibrillae running alongside the fat-cells and surrounding them (Fig. 30), that one could safely venture the hypothesis that in ordinary adipose tissue

every fat-cell is innervated or is at least under the influence of the efferent sympathetic system.

To conclude this chapter your attention is directed

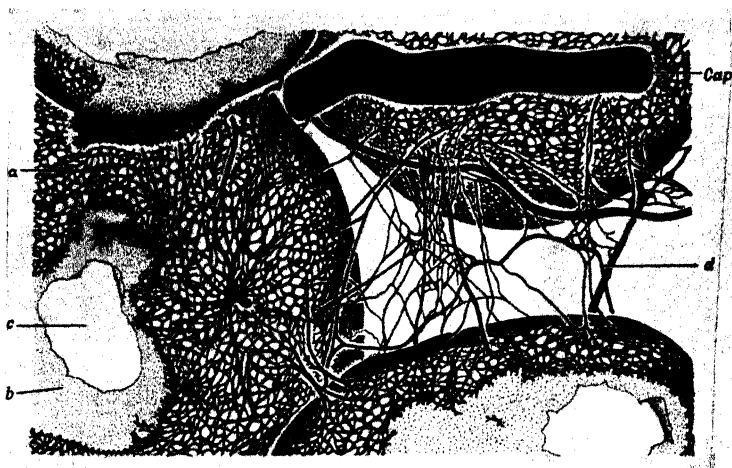


FIG. 31. Fat-cells with covering of reticular fibres. After Nageotte & Guyon, 1926. No nerve-fibres coloured.

to three figures, 29-31, two of which have been mentioned already. In Fig. 29 is the drawing made by Dogiel nearly forty years ago of nerve-fibres surrounding fat-cells. The nerve-fibres are stained with methylene blue, and there can be no doubt as to their being nervous in nature. In Fig. 30 is shown a drawing from a silver preparation of fine varicose fibres surrounding a fat-cell from human fat-tissue. Both preparations look essentially the same, and there would appear to be no doubt as to their both being of a nervous nature. In Fig. 31 is a picture by Nageotte of the reticular covering of fat-cells. It presents an entirely different aspect, and it would seem to be impossible to confuse the two kinds of fibre. On the contrary, Nonidez suggested that what was described as the sympathetic ground-plexus was in reality nothing but a system of

reticular fibres, that is a connective tissue formation. When it is seen that the varicose strands of fibrillae covering fat cells, visible in Fig. 30, are directly continuous with the various anastomosing bands of the ground-plexus, which could be established with the greatest accuracy, we may safely conclude that this plexus is entirely nervous in nature and has nothing to do with connective tissue formations, although in some places one may get a picture of connective tissue structures which somewhat resemble the pictures drawn of the sympathetic ground-plexus here described.

Hence it would seem that there is justification for drawing the conclusion, formulated above, that there is in the different tissues of the body a very rich and dense nervous plexus of a sympathetic efferent nature. It brings every element of the body into connexion with the sympathetic nervous system, and must be of fundamental importance for the maintenance of metabolism. It also maintains harmony between the body tissues themselves. This is the conclusion for which we have attempted to bring evidence in this chapter.

In the third chapter it is proposed to discuss the ways in which this connexion may be established, how and under what conditions it works, and the role of the sympathetic ganglion cells in the establishment of the wonderfully harmonious working of the organism.



## CHAPTER III

### THE PROBLEM OF THE 'INTERSTITIAL CELLS' IN THE SYMPATHETIC NERVOUS SYSTEM; THEIR RELATION TO NEURONES, AND THE INNERVATION-IMPULSE AS A HUMORAL CHANGE IN THE TISSUES

IN the second chapter some details of the sympathetic ground-plexus in different parts of the body were described, its richness and ubiquity, the important part it must play in metabolism and in the maintenance of functional harmony throughout the body. That it plays an important role is certain, but what is its role?

The experiments of Cannon described in the second chapter should act as a warning against speculation. During the course of a very interesting summary on the afferent paths for visceral reflexes, Ranson (1921) discussed the influence of the elements of Auerbach and Meissner plexuses on the movements of the walls of the stomach and the intestinal canal. He states that 'since next to nothing is known about the structure of these plexuses and the interrelations of the nervous elements which compose them, the problems relating to the control of the movements of the alimentary tract are very baffling'. Even now, fifteen years later, this admission is, we must confess, still true.

What is known of the termination of the sympathetic end-fibres of the intestinal plexuses on the musculature of the intestine? What is the function of the ganglion cells scattered singly or in groups throughout this plexus? Are they the only neuronal elements inside the intestinal wall; if so, how do their cell-processes end?

We know that the impulses given by elements of the sympathetic plexus are of a more general nature than those given by somatic neurones and their endings.

We know from the investigations of Dale and Adrian and their followers the importance of a humoral transfer of the sympathetic stimulus, and of the formation of specific hormones such as acetylcholine, adrenalin, or sympathin. Interesting observations were published in 1936 and 1937 by Roussy and Mosinger. Their distinction between *neurocrinie* and *neuricrinie* is certainly worthy of attention, as is their discussion concerning the value of humoral transfer. Histology has to procure a sound and solid anatomical basis for these physiological facts. Now it is assumed by most authors that an independent cell-process of a sympathetic ganglion cell simply ends on the surface of a smooth muscle-cell. However, these exceedingly small knob-like endings are found so rarely that Stoehr came to the conclusion in 1931 that only one in about a hundred smooth muscle elements receives such an ending. How then is it possible that a sufficient amount of, let us say, humoral energy is produced by these rare end-knobs for the contraction process which follows the nerve stimulus?

In smooth musculature a collective contraction of a large number of muscle-cells is even more necessary than in cross-striated muscles, and an innervation by exceedingly small end-knobs, supplying only one per cent. of the contractile elements, would be very difficult to bring into line with physiological facts and theories, especially with the observations on the humoral mechanism of contraction, which call for an innervation modus on every element of the musculature.

What is needed is simply a synapse: that is, a distinct end of argentophile neurofibrillar substance; a place where the impulse given by the nerve-fibre may be changed, *eine Umwertungsstelle der Erregung*, as it was called some years ago. This may be an end-knob or longer stretch of living substance, a *wirksame*

*Strecke*, as is so clearly seen in the more complicated sensory corpuscles which often contain a bewildering maze of neurofibrillae, but it has to be present on every element of the contractile substance (cf. Gaddum and Dale).

The term 'synapse', as is well known, has mainly a physiological meaning. In the synapse the stimulus is changed and remoulded, there is delay in the transmission of a stimulus through a reflex-arc, which is referable to transmission across the synapse. Certain drugs act specifically on the synapse, such as curare, nicotine, &c. In a synapse the stimulus is polarized and made irreversible; thus its physiological meaning is clear, and its fundamental importance in any conception of the physiological transmission of a nervous stimulus indisputable. We cannot dispense with it even in an interpretation of sympathetic stimulation of a general nature.

This physiological conception of the synapse should of course have a sound histological basis.<sup>1</sup> It may be a surface of separation between neurone and neurone. In the reflex-arc, at least in the spinal arc of the vertebrates, it may be a transverse membrane across the conductor. 'Even should a membrane visible to the microscope not appear, the mere fact of non-confluence of the conductive element of one cell with the conductive part of the other implies the existence of a surface of separation' (Sherrington). In the sympathetic system such a membranous synapse is not so easily understandable, and it all depends upon the fluid or non-fluid condition of the conducting element.

At all events the synapse must be composed of living and therefore alterable substance, and not of a lifeless 'sticky substance', *Kittsubstanz*, as was postulated in

<sup>1</sup> The question of the synaptic junctions is more fully discussed in the last chapter.

the original neurone theory. It may be a long stretch of living substance, it may even be present in the form of a distinct living differentiated, net-like structure, but it must be living substance and not inert material (Judson Herrick).

The neurofibrillae, although they may have to do with metabolic influences in nervous elements, as hypothesized by Parker (1929), perhaps in the form of 'chains of ionic readjustment' (Parker), certainly have to do with the conduction of the nervous impulses. They are present in the living nervous element (Weiss, Levi, 1936), and have even been photographed by Weiss in living ganglion cells in a tissue culture. The nerve impulse may be in the nature of a progressive wave of ionic readjustment in some membranous layer of the neurone (Lillie), evoking a humoral change in the living substance of the innervated element. The synapse must, however, consist of living substance in the form of a connexion of the neurofibrillar structures of the two elements concerned. In the last chapter the nature of synapses will be discussed more fully. Here it is only necessary to emphasize the unquestionable importance of a synaptic junction even in sympathetic plexuses, and of the difficulty of constructing a sound histological basis for synaptic junctions in the sympathetic nervous system with its humoral transfer of the nervous stimulus.

To understand this difficulty it is first necessary to examine the results of a series of very interesting physiological observations started in 1904 by Magnus and continued by Bayliss and Starling in 1910, Magnus (1914), Gunn and Underhill (1914), Alvarez and Mahony (1922), Gasser and van Esveld (1926). Bayliss and Starling had found that when the intestine was painted with cocaine and nicotine true peristaltic movements ceased, but pendulum movements continued.

They concluded that the latter were myogenic in origin. Magnus had come to the opposite conclusion, notwithstanding the fact that the isolated intestine may continue to beat rhythmically in a solution of nicotine of 1 in 1,000. This certainly seems to suggest that either the movements were independent of nerve-ganglia or that these ganglia were unusually resistant to nicotine. In his later experiments, however, Magnus found that when all the ganglion cells were removed from an isolated strip of intestinal circular muscle it lost the power of rhythmic movement. He therefore concluded that the ganglion cells were an indispensable factor for rhythmic movements.

Gunn and Underhill (1914) came to the opposite conclusion, and showed that even the isolated circular muscle of the cat's small intestine possesses the power of executing rhythmic movements when it is completely separated from the longitudinal muscle and from the submucosa and mucous membrane.

Van Esveld in 1926 isolated strips of the circular muscle of the cat's intestine as carefully as possible and experimented upon them after having freed them from all ganglion cells (see Fig. 32). After the experiments the strips were examined histologically and it was found that a strip of this muscle which did not contain a single ganglion cell was still able to perform regular rhythmic movements. The movements of such a strip without ganglion cells were still susceptible to the action of drugs, and altered by electrical stimulation. They still showed the characteristics of rhythmic movements of neurogenic origin. Van Esveld showed that in such strips, isolated from the body and kept in a refrigerator for eight to nine days, the plexus of neurofibrillar strands was still present. When these disappeared, rhythmic movements ceased altogether. Is it then possible to conclude that rhythmic movements

in a strip of smooth muscle deprived entirely of its ganglion cells are undeniably of myogenic origin? Van Esveld denied the unassailability of such a conclusion.

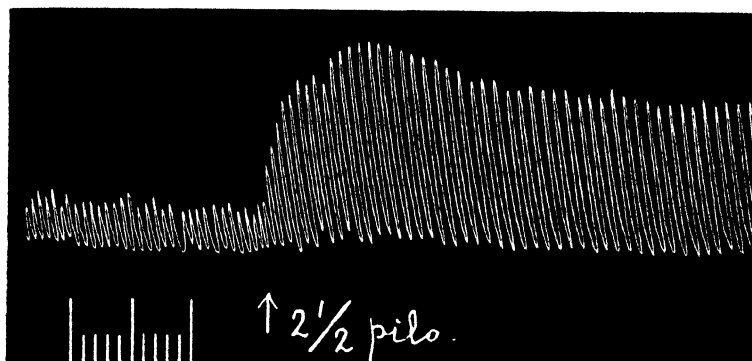


FIG. 32. Contraction curve of strip of smooth muscle of the intestine of a cat, without ganglion cells. After van Esveld, 1928. The arrow indicates moment of addition of pilocarpine (1 : 30,000). 1 cm. = 90 seconds. After the experiment the piece was examined histologically, and did not contain a single ganglion cell.

He showed that, even after all ganglion cells of the plexus of Auerbach (see Fig. 33) and of Meissner have been removed, we have no right to conclude that such a strip of tissue is entirely without nervous elements, and drew attention to the so-called 'interstitial cells' of Cajal, which Lawrentjew in 1925 had again placed in the centre of the discussion by maintaining that they formed the real endings of the sympathetic plexus. As these cells lie scattered throughout the whole muscle layer, it was impossible to remove them from the muscular elements and thus the problem could never be solved. If this is so, these interstitial cells deserve thorough examination and discussion, for they must be present everywhere in the body and their physiological function must be of fundamental importance. An attempt has been made to investigate them as carefully as possible in my own laboratory. They have

already been mentioned in the course of the second chapter, but in this chapter they will be discussed more fully to see if it is possible to arrive at a more definite

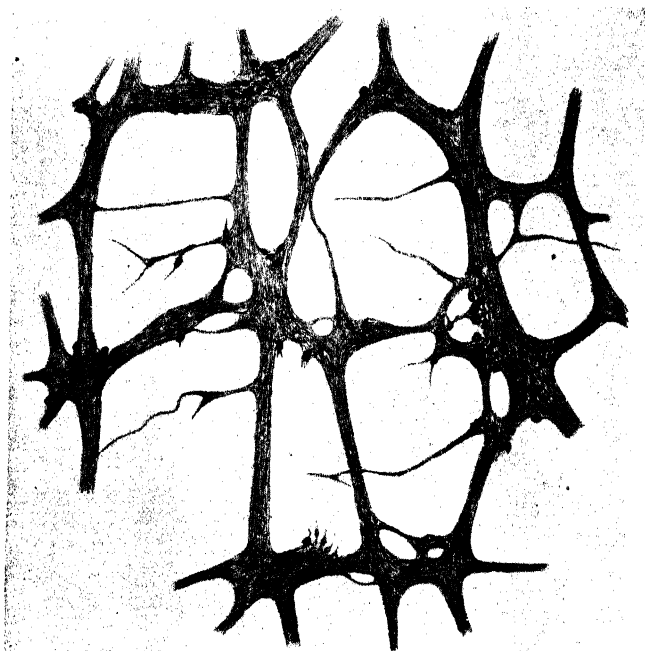


FIG. 33. General view of plexus entericus in man. After Stoechr.

conclusion concerning their morphology, their probable physiological value, and their origin. If they are of real morphological value, then the whole problem of the synapse, which was outlined in a few words at the beginning of this chapter, must be centred upon these elements and must here find its solution.

To understand the notion of the interstitial cells aright we must go back to the original description of Cajal, for Cajal has stuck to his original conception during his whole scientific career, and even in his last book on the structure of the nervous system, which

appeared during the year of his death in 1935, he seems still convinced of the truth of his description of the year 1894, just as he was convinced in 1911 and 1924.

As is well known (see Fig. 33) there is a sympathetic nerve-plexus in the wall of the intestine which consists of two parts—a coarser one, lying between the circular and longitudinal musculature, the plexus of Auerbach, and a finer one, lying in the submucosa, the submucous plexus of Meissner. Bloom (1936) gives the following clear description of these plexuses based entirely upon the splendid work of C. J. Hill (1927), who gave a very detailed and elaborate description of these nervous formations as they appear in first-class methylene blue preparations:

‘In a surface view the ganglia of the myenteric plexus appear as massive, angular or star-shaped accumulations of nerve cells. They are connected with one another by thick or thin stands of nonmyelinated fibres of both extrinsic and intrinsic origin. The ganglia of the submucous plexus are thin and flattened, and their cells are grouped close together. They are also connected by a multitude of bundles of fibres arranged as in the ganglia of the myenteric plexus. Many varieties have been described among these nerve cells of the enteric ganglia. It is possible, however, to reduce the number of all varieties to two principal forms, which in any particular case may present differences in their secondary characters. The first type occurs exclusively in the myenteric plexus. It is a multipolar cell with short dendrites which terminate in brush-like arborizations on the bodies of cells of the second type in the same ganglion. The axon enters a fibre bundle as a fine, non-medullated fibre; it can be traced for a considerable distance through the neighbouring ganglia and fibre tracts and is supposed to form connections with cells of the second type in other ganglia.’

According to Hill and Bloom the cells of the second type are far more numerous and show great variations in their form. Their dendrites vary in number and



are often missing (unipolar cells). According to Hill unipolar cells are even more numerous than other forms of the second type. The dendrites, when present, divide dichotomously in the ganglia of origin or in other ganglia and terminate in diffuse receptive endings (often in the form of 'dendritlamellae', Lawrentjew and Stoehr, ref.) in relation with nerve-cells of the first and second types (Hill). The axon enters a fibre-bundle and divides: its branches after pursuing separate courses terminate, as far as can be seen, in the circular or longitudinal layers of muscle. They have the usual connexion (Hill) with individual smooth muscle-cells. Thus the neurones of this second type are motor in nature according to Hill and most other observers. They may possibly have something to do with the vagus system (Hill, Lawrentjew, Kolossow, and Sabussow).

The single process of the unipolar cells divides into two branches, one of which passes out to the muscularis; the second could not be followed to its termination (Hill). The cells in the myenteric plexus seem to supply the muscularis externa in every case, as far as could be made out. Those of the submucous plexus supply the muscularis mucosae and the muscles of the intestinal villi according to Hill and most observers, including text-books (Bloom).

As mentioned already in the second chapter (p. 52), besides the two kinds of cells just mentioned, Cajal described a third type of cell in the enteric plexus and also scattered in the submucosa and interior of the villi, which he called *neurones sympathiques interstitiels*, interstitial cells (see Fig. 34), small multipolar cells with a finely vacuolated cytoplasm and numerous short, richly branching, varicose processes, which interlace or anastomose to form an irregular network. They seem to be connected with the smooth muscle elements. 'Il résulte de cette description qu'il existe dans les

muscles lisses deux sortes d'arborisation nerveuses; les principales qui proviennent des grandes cellules ganglionnaires du plexus d'Auerbach et qui sont en

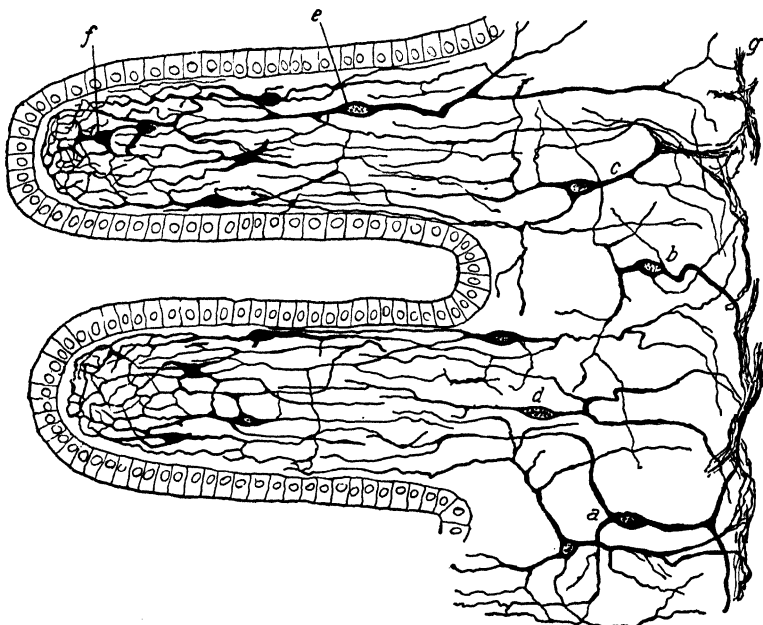


FIG. 34. Interstitial cells and plexus in the mucosa of the small intestine of Cobaya. After Cajal, 1911. *g* = plexus of Meissner.!

même temps les plus nombreuses, et les accessoires qui émanent des cellules interstitielles' (Cajal, 1894). As they lie in the spaces between the bundles of the nervous plexus Cajal speaks of them as an 'interfascicular plexus'. There would be therefore a double innervation of the smooth muscle elements, and Cajal puts forward as a very cautious hypothesis the idea that the interstitial elements are influenced by the sympathetic fibres entering the intestinal wall. He did not observe a distinct connexion of his interstitial cells with the classic sympathetic elements. They seemed to form

a syncytial arrangement, anastomosing with each other everywhere; 'C'est donc dans l'intestin que nous verrons se produire pour la première fois de véritables réseaux anastomotiques' (Cajal, 1894), but as a convinced neuronist he added: 'mais n'oublions pas qu'il se pourrait très bien, que les anastomoses ne soient qu'apparentes et qu'elles ne représentent en réalité que de simples chiasmas ou entrecroisements de fibres fines émanées des fascicules voisins'. In the years following, these interstitial elements were studied by a number of authors and, however they regarded them, they all agreed that they form a syncytium (cf. Tinel, 1938). And so we see that in his description of these elements in 1911, Cajal himself relinquishes his reserve of 1894 and simply states that the interstitial elements form a syncytium with anastomosing branches (cf. Cajal in 1935).

As mentioned already, since the original description by Cajal of these elements they have been studied by a number of authors. Dogiel (1895) studied them with methylene blue and declared them to be of mesenchymatous nature, connective tissue elements. In 1899 he described them again as being of the nature of connective tissue elements. He was followed in this by Heidenhain, Carl Huber, Kuntz, Johnson, Cole, and Tiegs. This view is expressed in the clearest manner by Johnson (1925) when he says: 'the syncytial network bears no resemblance to nervous tissue, and although it occupies the intermuscular space in company with the mesenteric plexus, it extends beyond the limits of this space, between the muscle bundles. It is undoubtedly composed of connective tissue, perhaps slightly modified to meet the functional demands of its somewhat unusual anatomical position.' What this modification is is not indicated.

Other authors are less dogmatic in their descriptions;

others follow the line taken by Cajal. La Villa described these interstitial elements as being of nervous nature and origin (1897, 1898). Bethe (1903) described a ground-net of a definitely nervous nature in the mucosa of the frog's mouth, which he homologized with the interstitial cells of Cajal. Erik Mueller described the same thing in 1921. Leontowitsch described a syncytial nervous ground-net in the wall of arteries containing small nerve-cells, which were identical to the interstitial cells (1927).

Muench (1905) and Schock (1910) described them as occurring in great numbers in the very loose connective tissues of the iris. Their description and opinion were followed by Wolfrum in 1931 and partly by myself in 1936.

Elements of the same nature were described after staining with methylene blue in the wall of the intestine by Okamura (1935), and lastly by Schabadasch (1935).

In 1937 they were studied as accurately as possible in my laboratory by Leeuwe, as a continuation of my own investigations. In the veterinary laboratory they have been studied very accurately by Meyling in the wall of the aorta and in the glomus aorticum.<sup>1</sup> All these authors came to the conclusion that they are nervous in nature. An intermediate position was taken by Bloom, who admits that they are probably of nervous origin, but that they might possibly be of a microglial nature (1931). This, however, is improbable, since Cajal described a neurofibrillar structure in their protoplasm, which even changed its aspect in hibernating animals (Cajal, 1911).

Thus we see that the problem is not as yet definitely settled, but that the trend of the observations is in the

<sup>1</sup> In 1938 they were very elaborately described by Tinel in his book on the vegetative system. They occupy an important position in his observations.

direction of declaring them to be of nervous nature and origin but not stating their function.

As has been mentioned already, Lawrentjew in 1926 and above all van Esveld in 1926 and 1928 tried to secure a more dignified position for them and put them into the forefront of the discussion by declaring them to be the real and only terminal elements of the sympathetic end-formation, real *neurones sympathiques interstitiels* as they were originally called by Cajal.

According to Lawrentjew's description (see Fig. 18) the interstitial elements are the important element of the end-formation of the sympathetic plexus, because they are its constant syncytial terminal elements. From these elements grow out the endings on the smooth muscle-fibres, &c. At the end of the so-called tertiary strands of the enteric plexus he always finds distinct branched elements of a peculiar shape, which remind us forcibly of the shape of the interstitial cells as originally pictured by Cajal (cf. Fig. 34).

According to Lawrentjew the finest branches of the sympathetic plexus show a syncytial structure, the neurofibrillar strands being enclosed in a protoplasmic sheath with dispersed nuclei of Schwann, but without definite cellular sheaths. Exactly the same thing was maintained in the same year by Nageotte and Guyon for the nerves of the human cornea. Lawrentjew states that when such a nervous strand is followed in its course between the muscle elements an accumulation of protoplasm with a nucleus enclosed in it is always met at distinct points along this course. From this point numerous branched processes project in different directions, the bundles of neurofibrillae in these processes being still enclosed in a thin layer of protoplasm (*Protoplasmastränge*).

These are the interstitial cells, and from them the ground-bundle of neurofibrils may pass on to other

interstitial elements, always maintaining a syncytial arrangement, or give off small end-knobs, the motor endings on smooth muscle-fibres. Thus, according to Lawrentjew, there may be several interstitial elements lying one after another in syncytial continuity in the course of a sympathetic end-fibre before its real ending on the smooth muscle-fibre is reached. Van Esveld agreed with this conception and showed, by the remarkable pharmacological experiments described above, the high physiological importance of these elements. Leontowitsch, Schabadasch, and others agree with these suggestions, and in a series of contributions to the histology of the end-formation of the sympathetic system, which were discussed more fully in the second chapter, it was shown by the author that these interstitial elements are constant in structure, and that they are to be regarded as true interstitial parts of the sympathetic end-formation. From them grow out intermittent synaptic structures, the intraprotoplasmic so-called 'periterminal network', by which the nervous impulse is transmitted to the various organs of response (1934-6).

The above authors mostly used silver-methods, but Leeuwe (1937) and Meyling (1938) succeeded in staining them with methylene blue, which enables one to study them in thicker sections and in total preparations of thin membranes, and thus the better to follow their course and connexions. Leeuwe studied the interstitial elements in the enteric plexus of different mammals (cat, cavia) and of frogs, and in the submucous tissue of the frog's mouth, the region where Bethe had described his nervous ground-net. Contrary to Abraham (1936), who could not find this network in the mucous membrane of the mouth, Leeuwe succeeded. He used a modification of the methylene blue method and light-filters, which brought out even the finest blue-stained fibrillae

with the utmost sharpness, and showed that even here the network described by Bethe existed. Most of his observations were made on the enteric plexus of frog larvae, new-born mammals, and full-grown animals. In frog's intestine the structure of the enteric plexus was found to be similar to that in mammals, and in total preparations of the intestine of frog larvae and small mammals even the development of the interstitial elements could be followed with exactness. They grow out from the clusters of the ganglion cells of the developing sympathetic plexus, radiating from them as distinct elements with branching processes, but always in syncytial continuity. They thus spread out into the musculature until they reach the muscle-cells themselves. It was even possible to follow the development of the neurofibrillar structure of the syncytial elements. In this respect it was of interest that the neurofibrillar structure, which appears in these elements, did not begin in the elements of the plexus from which the interstitial syncytium had grown out, i.e. the ganglion cells, and spread from there into the syncytium. According to Leeuwe the neurofibrillar structure first showed itself at the terminations of the elements of the end-formation just where the strands came into connexion with the muscle-cells. From here it became visible passing backwards, reaching in the end the elements of the primary plexus which were already fibrillated.

Thus, during this phase of the development, the end-formation of the syncytial plexus of the developing interstitial elements in which neurofibrillae were visible were connected with the elements of the primary plexus, in which neurofibrillae were also visible, by a series of syncytial non-differentiated elements, which gradually became fibrillated from the periphery towards the centre.

By a very sensitive method of staining Leeuwe could even show that these interstitial elements possessed Nissl-bodies in their protoplasm; just like ordinary ganglion cells; in the same way the interstitial elements showed other features of ordinary ganglion cells, for instance with regard to the effects of the oxidase- and peroxidase-reaction. The  $\pi$ -granules, which form characteristic elements in the protoplasm of lemnoblasts, cells of Schwann, could not be detected inside interstitial cells. All these points brought Leeuwe to the conclusion that the so-called interstitial cells have to be regarded as belonging to the group of ganglion cells and not to that of the lemnoblasts, and that they are derived from true ganglion cells by a series of intermediate forms. They are always in syncytial connexion with each other and with true ganglion cells of the sympathetic plexus, and must be regarded as a kind of primitive neuron element.

The author had arrived at approximately the same conclusion the year before by a study of the plexus in different vertebrates, though he did not feel entitled to draw such a sharp line of separation between the neuron elements and the so-called lemnoblasts, or sheath-cells, as Leeuwe does (Boeke, 1935).

In several tissues which are particularly adapted to these studies, as, for instance, the tissue surrounding the muscle-spindle fibres (Boeke), the cornea and the iris (Boeke, Nageotte, Stefanelli), the neuroplasm, in which the neurofibrillae lie imbedded, is not to be separated histologically from the protoplasm of the surrounding lemnoblastic elements.

These differences are, however, of minor importance. The chief point of value is the recognition of the interstitial elements as specific structures in a syncytial arrangement and in definite connexion with true ganglion cells of the sympathetic plexus, which means that



they form a nervous element distinguishable from the other ganglionic elements, and with a special function.

But even if we acknowledge the interstitial elements as a distinct reality, the question arises, how then are they to be regarded, what is their morphological value, and how are they to be interpreted? What is their functional, or physiological, value? From what has been said already, it will be obvious that our conception of the physiological significance of the sympathetic plexus, of the independent character of the sympathetic end-formation, and of its intrinsic function as has been shown by the pharmacological experiments of van Esveld, will depend upon our interpretation of these elements.

The final discussion may be divided into four parts.

*Part I.* At the beginning of this chapter attention was called to the necessity for a true synaptic junction between the ends of the argentophile neurofibrillar nervous structures and the living substance of the innervated elements.

This synapse must be a junctional region, a place where the nervous stimulus may be remoulded, polarized, &c., *eine Umwertungsstelle der Erregung*. It is difficult to ascribe this property and the formation of a specific hormone, necessary for the humoral transfer of the nervous stimulus, as claimed by modern physiology, to a tiny end-knob, which is present on only one in about a hundred smooth muscle-cells, as described by histologists (Stoehr, 1934). The need for a stronger mode of innervation is obvious. Not only in the enteric musculature, but also in the wall of the arteries is felt the need for a mode more adequate to fulfil the claims of modern physiology of innervation than the one recorded here. Even in somatic innervation, as soon as a sensory corpuscle has to fulfil a more complicated purpose, that is to say, that by its structure

and situation it gives the impression of being able to respond to stimuli of a more delicate nature, such as may be attributed to sensory corpuscles of higher

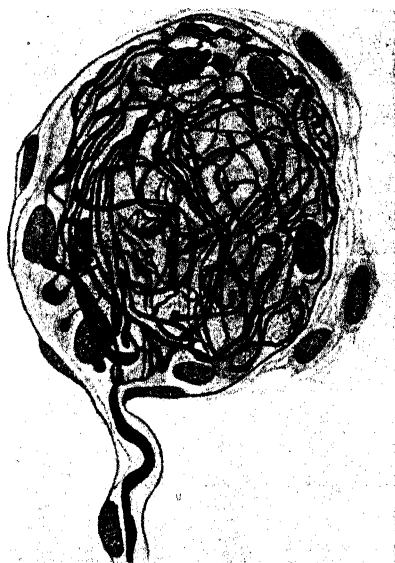


FIG. 35. End-bulb of Krause from human conjunctiva. After Boeke, 1938.

order, it shows an enlargement of the surface of its neurofibrillar structure (compare Figs. 21 and 35) in order to convert the most delicate impressions to active stimuli. In this way the complicated neurofibrillar structures of the corpuscles of Meissner, Krause, Ruffini, Grandry, or Herbst may find an explanation. In the end-bulb of Krause of Fig. 35, for example, the whole mass of convolutions may be compared with the 'active stretch' of synaptic value.

A knob-like ending is not found here, but an 'active region', a *wirksame Strecke* of the neurofibrillar end-formation (see Fig. 35). Thus, to give another instance,

in a Meissner's corpuscle with its complex neurofibrillar structure, its convolutions with large ribbon-like, flattened expansions, gradually breaking up into numerous thin twigs, forming most complicated loops and twists (Fig. 21), the conducting elements must be peculiarly adapted to the registration of very delicate nervous impressions, the entire 'active region' of the neurofibrillar structure responding as a receptive surface.

Now in the sympathetic end-formation it would seem that the need for such an elongated 'active region' of the neurofibrillar apparatus would be felt even more strongly. Here the nerve-impulse, either motor or sensory, has not such a local, individual character as in somatic innervation. There is more need of collaboration between the different elements over a comparatively larger area than in somatic innervation. Sympathetic innervation has a more general character, and it is obvious that the more the innervated elements are in constant collaboration, the more they are normally acting together and not individually. Hence the more the need for a mode of innervation acting simultaneously over a large area such as an 'active region' of the neurofibrillar end-formation, and not by means of rare end-knobs only in connexion with the innervated tissue elements at rare intervals.

We thus have to distinguish an 'individual innervation' and a more 'plexiform innervation'.

A curious example, which illustrates the importance of this distinction, is given by the mode of innervation of the intrinsic eye-muscles, which regulate the process of accommodation and the width of the pupil, the ciliary muscles, and the muscle of the iris. In mammals these muscles are composed of smooth muscle-fibres, arranged in bundles and small groups, which form a dense, net-like framework towards the posterior edge

of the orbiculus ciliaris. The muscle-fibres can only be separated with difficulty and appear to possess a syncytial structure, the myofibrillae running from one fibre into another without interruption. These groups of muscle-fibres always act together and the whole process of accommodation and regulation of the width of the pupil depends on this regular co-operation.

In man and in different mammals which the author investigated a very complicated net-like nervous plexus is found in the ciliary muscle. It has ring-like nerve-endings inside the muscle-cells and branches which anastomose everywhere with each other. The network is extremely rich and present throughout the whole extent of the ciliary muscle, and one is entitled to say that every muscle element and every bundle of syncytial muscle-cells is innervated by the selfsame network of plexiform anastomosing strands of neuro-fibrillae. The same is true for the nerve network in the muscle of the iris, which provides the very best instance of what one might call a 'plexiform innervation' (Boeke, 1916, 1933).

Now in birds, as is well known, it is found that the ciliary muscle and the muscle of the iris are composed of cross-striated muscle elements, which at first in very young animals hang together in a truly syncytial manner, but which gradually become more and more independent of each other. In full-grown birds they are independent elements, often separated by rather wide spaces (Boeke, 1933). They often branch in a T-like fashion. And it is of interest for the whole conception of nervous innervation that, when we study the nerve-supply of these elements during their development, we see at first a real unquestionable plexiform innervation. All the nervous fibrillae hang together, and from this network true independent motor end-plates, each innervating a single muscle-fibre, are seen to develop

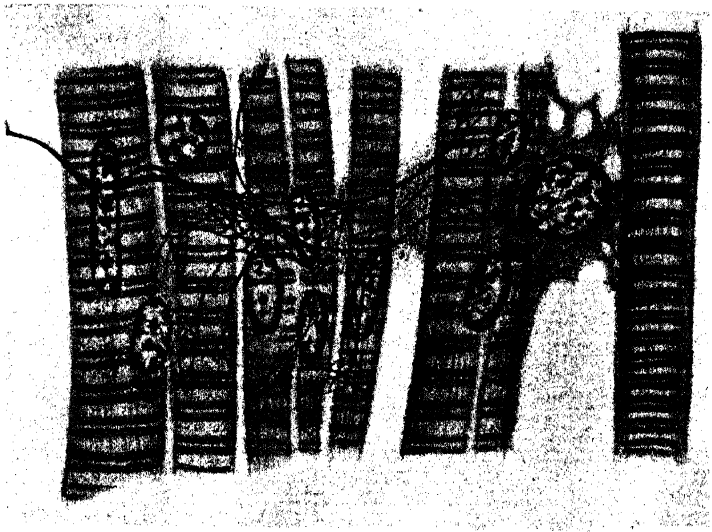


FIG. 36. Plexiform innervation of the eye-muscle of a young bird, *Falco subbuteo*. After Boeke, 1927.

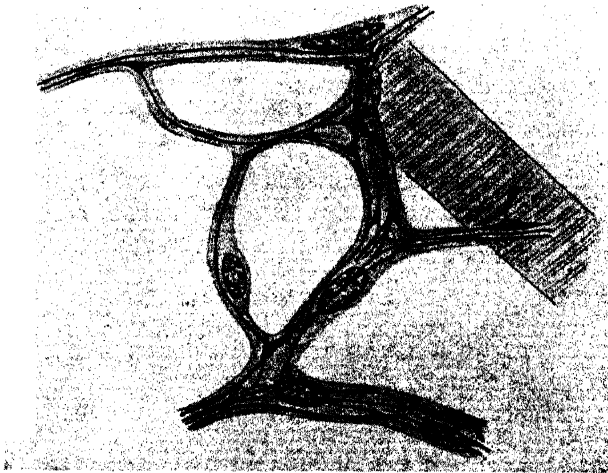


FIG. 37. Syncytial stage in developing muscle-nerves, tongue of a mole embryo. After Boeke.

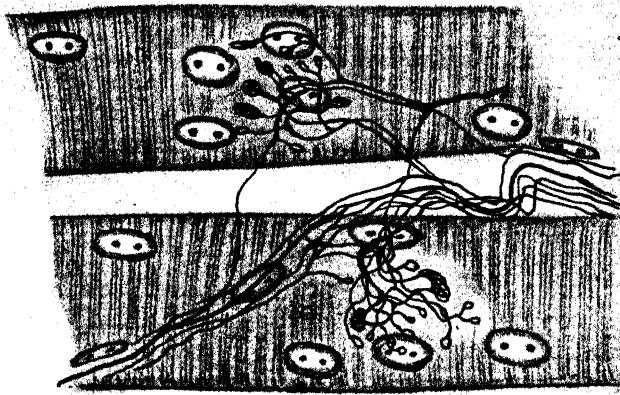


FIG. 38. Cross-striated muscle-fibres of the tongue of a young mouse, with formation of end-plates by multiple nerve-fibres. After Boeke, 1927.

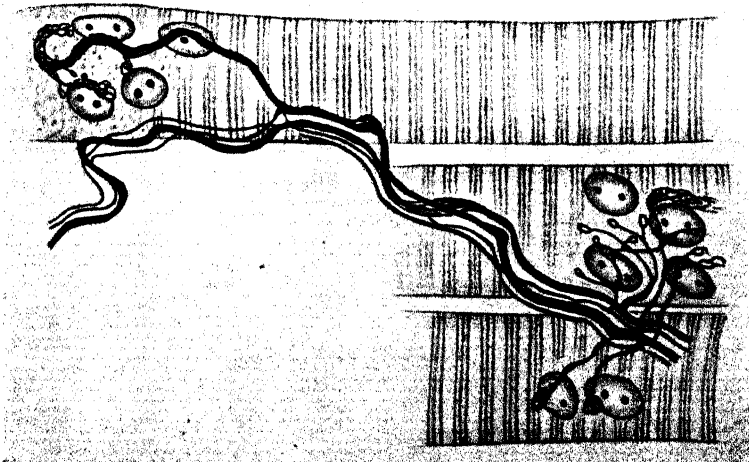


FIG. 39. Formation of definite motor end-plates in the tongue of a young mouse. After Boeke, 1927.

gradually. As soon as the muscle elements appear as independent striated fibres, each muscle-fibre is innervated by a single motor end-plate. Here we are able to follow the formation of true individual innervation from a plexiform innervation in conjunction with the gradually advancing independence of the innervated elements themselves (cf. Fig. 36).

It is of interest in this connexion that when we study the development of common striated muscle-fibres in the tongue and in the extremities we find the same thing, the intercalation of a true syncytial stage in their innervation between the first outgrowing process of the motor-nerves and the formation of true independent motor end-plates. Even here we find an initial plexiform innervation and from this the definitive individual innervation arises (cf. Figs. 37, 38, 39).

*Part II.* An exceedingly difficult question to elucidate is the connexion of sympathetic non-medullated nerve-fibres to elements of mesenchymatous origin. Goormaghtigh pointed out (1924) the 'close bonds of relationship which unite the ganglion cells of the spinal ganglia, the Schwann-cells and the chromaffin cells in the adrenal gland'.

Masson and Berger showed (1923) that the same sort of relationship exists between the sheaths of the non-medullated nerve-plexuses and the interstitial cells of the ovary and of the testicle.

In the pancreas van Campenhout (1925, 1927) has studied the intimate connexions which certain cells of the primary islands of Laguesse (Langerhans) make with the plexus of sympathetic nerves. These relations concern only the satellite apparatus.

In the cornea Nageotte and Guyon (1926) described a network of sheaths for the corneal nerves which envelop a number of different neurites. These fibres make contact with certain connective tissue cells; according

to Nageotte their contacts are only superficial, but even he agrees 'that these nerve fibres sometimes when in contact with a cell throw out extremely fine collaterals which follow one border of the cell', and he adds: 'some writers speak of an innervation of connective tissue cells, and Guyon and I have made observations that are not unfavourable to this interpretation' (1931).

Now in the frog and in birds<sup>1</sup> this connexion is so apparent as to leave no doubt as to its reality (Boeke, 1926, 1935). In the iris of mammals (monkeys) there exists such a close connexion between the sympathetic non-medullated nervous plexus and the apparent connective tissue cells that even as long ago as 1905 and 1910 these connective tissue cells were described as true interstitial cells of Cajal (Muench, 1905; Schock, 1910; Wolfrum, 1931). In the iris of monkeys and of man we find the most interesting loose connective tissue the author has ever seen. It contains, at least in the so-called vessel layer, numerous blood-vessels, and the spaces in between them are filled with such loose, sponge-like connective tissue that at first sight in ordinary preparations only the black or brown branched chromatophores connected by thin spiderlike fibroblasts are seen extending with long branches in an apparently empty space, filled solely with fluid.

Only when the connective tissues are stained very carefully, we see that this space is filled with very loosely arranged wavy collagenous fibrillae. In this loose connective tissue, nerve-fibres run everywhere, and even the thin nerve-fibres are very loosely arranged. They form not only a plexus, but a real network, as can be seen without doubt in silver preparations and after staining with methylene blue. This network of neurofibrillar strands is in such close connexion every-

<sup>1</sup> In 1938 Stefanelli showed that it is true for the reptilian cornea too.



where with the cells (Fig. 40) mentioned above, that one can only speak of a syncytial arrangement in which the neurofibrillae run inside the protoplasm of the cells.



FIG. 40. Nervous plexus in the iris of a *Macacus rhesus* with nerve fibrillae lodged in the protoplasm of stellate cells in protoplasmic connexion with stellate connective tissue cells. Bielschowsky-method. After Boeke, 1936. *Chr.* = chromatophores.

This syncytial arrangement is so apparent that even so long ago as 1905 and 1910 all these cells were identified (Schock, Muench, and later Lauber) with the interstitial cells of Cajal, and it was maintained by these authors that all the branched cells in this tissue were of nervous origin and nothing else but interstitial cells, and that every chromatophore was innervated by them. Expressed thus this statement is untrue, but it contains a nucleus of truth.

There is (Fig. 40) a close syncytial protoplasmic connexion between the finest neurofibrillae and the surrounding elements. In this way these elements are to be regarded as true interstitial cells. In carefully made preparations through an iris of a new-born macaque in which the chromatophores are not yet black but only greenish-brown transparent colour,

it was even possible to state with certainty that the chromatophores are innervated by the same delicate neurofibrillae. However, not every branched cell of

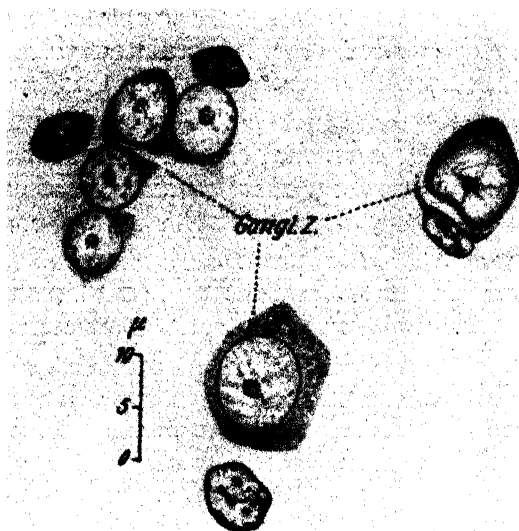


FIG. 41. Large and small ganglion cells in the iris of a *Macacus rhesus*, Nissl-bodies stained red.

the connective tissue stroma of the iris can be called an interstitial cell.

We find in the iris true ganglion cells with large round nuclei and multitudes of Nissl-bodies in their protoplasm (Fig. 41). These ganglion cells lie in groups in the loose connective tissues and are connected with the nervous strands. In silver preparations and in preparations stained with methylene blue we find small multipolar cells with a network of neurofibrillae inside their protoplasm in connexion with the neurofibrillar strands of the nervous network described above. They lie in a syncytial arrangement and in distinct

protoplasmic connexion with the branched cells of the connective tissue of the stroma of the iris.

Leeuwe was able to demonstrate that Nissl-bodies are present in their cytoplasm, which thus proves their nervous nature (Fig. 41). These elements are true interstitial cells of Cajal, as postulated years ago by Schock, Lauber, and Wolfrum (1931). Here in the loose connective tissue of the iris they can be studied with the utmost exactness, and they appear as small ganglion cells forming a syncytium connected and anastomosing everywhere with the cells of connective tissue origin mentioned above.

Whether one may speak here of an 'innervation of connective tissue elements', as Nageotte puts it for the cells of the cornea, it is difficult to say, but in the author's opinion it demonstrates the peculiar character of these interstitial cells as intermediate elements of nervous origin in protoplasmic connexion with elements of a true connective tissue character. They innervate the muscle elements of the iris, and together with the sympathetic plexus in which they lie must be of an efferent nature.

*Part III.* In the third place I want to call your attention to the curious nerve elements covering the intestinal wall of *Amphioxus lanceolatus*, which I described two years ago in the *Quarterly Journal of Microscopic Science*. Very little is known about the sympathetic nervous system of *Amphioxus*. The general opinion among scientists is that *Amphioxus* does not possess sympathetic nerves at all in the sense of the sympathetic plexus of the higher vertebrates. Only Van Wijhe (1913), Dogiel (1903), and Kutchin (1913) described delicate nerve-fibres on the wall of the pharyngeal bars and of the rectum. True ganglion cells were not found, but Dogiel described small triangular elements lying at the nodal points in the nervous

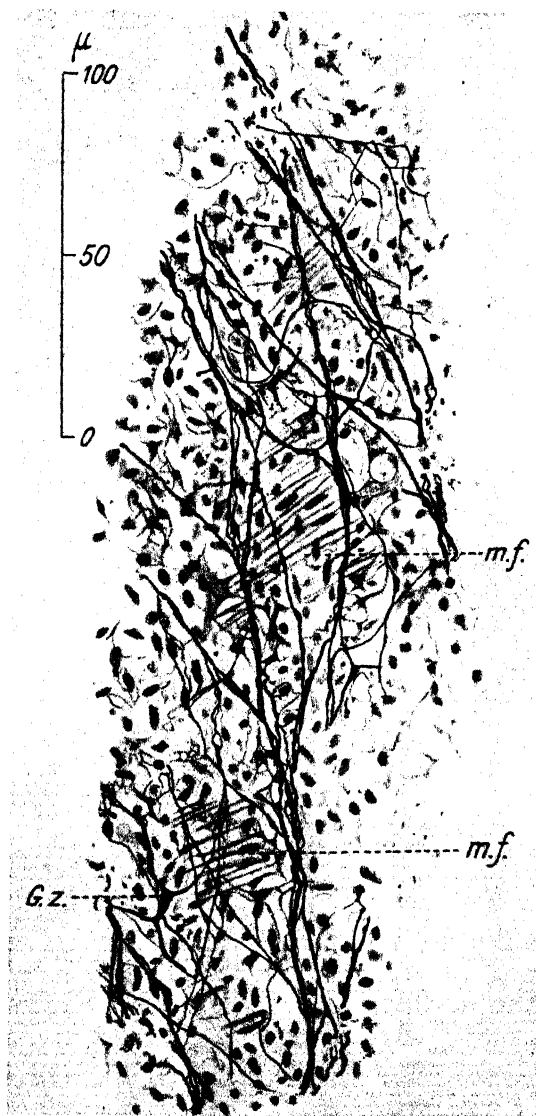


FIG. 42. The enteric plexus of an adult *Amphioxus*, as shown in a thin longitudinal tangential section through the wall of the intestine. After Boeke, 1935. *m.f.* = smooth muscle-fibres; *G.z.* = sympathetic ganglion cell.

plexus on the walls of the branchial bars, which stained with methylene blue and which he supposed to be ganglion cells. Van Wijhe found them in silver

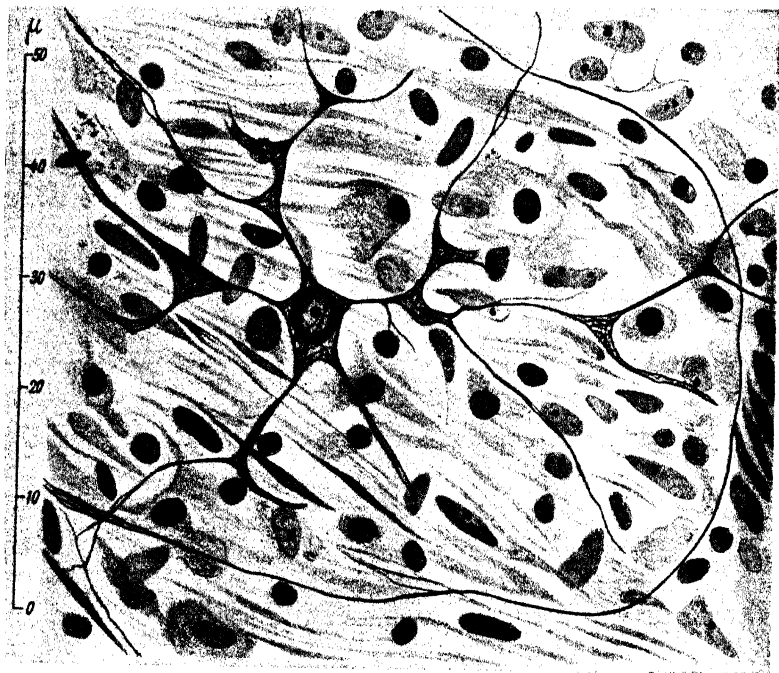


FIG. 43. Stellate ganglion cells from the wall of the post-hepatic intestine of an adult *Amphioxus*, with thin lamellar expansions of the dendrites (*Dendritlamellae*); see also Fig. 44. After Boeke, 1935.

preparations beneath the epithelium covering the liver and the post-branchial prehepatic intestine. He described them only cursorily in a footnote, paying but little attention to them.

When the wall of the liver-diverticulum and of the intestine is studied in silver preparations made as carefully as possible, preferably in longitudinal section which cut the thin wall of the intestine tangentially, we find an astonishing abundance of stellate multipolar

nerve-cells lying in a very rich and delicate nervous plexus, the enteric plexus. The complex nature of this plexus is well shown in Fig. 42.

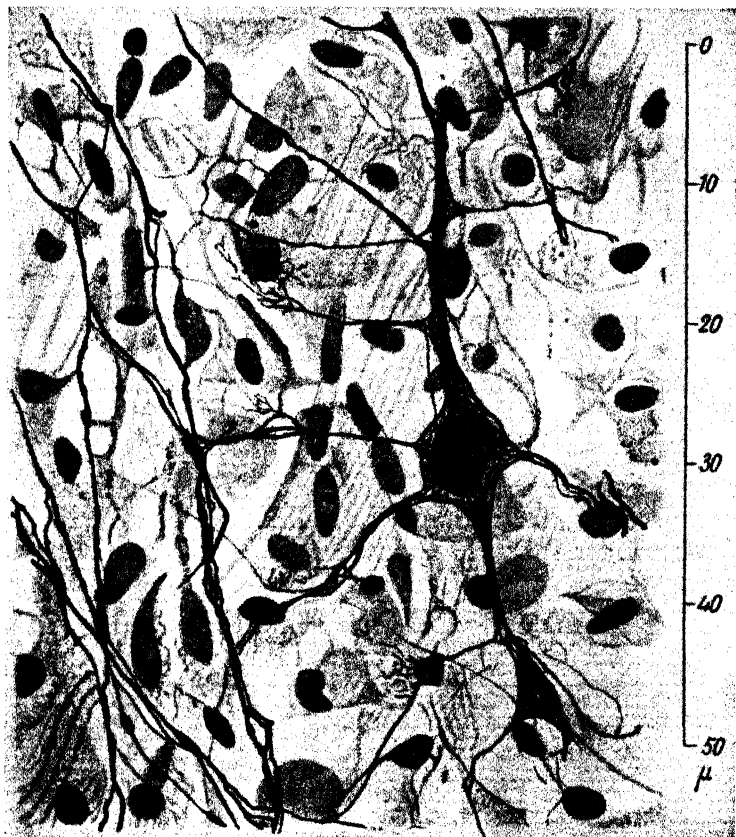


FIG. 44. Stellate ganglion cells from the wall of the post-hepatic intestine of an adult *Amphioxus*; see also Fig. 43. After Boeke, 1935.

The nerve-cells are very thin and flattened on account of their lying in the extremely thin membranous connective tissue covering the intestinal wall. They often present broader flattened extremely thin parts of their cell processes, comparable to the 'Dendrit-lamellae' described by Lawrentjew (1929) and Stoehr

(1932) in the dendrites of sympathetic ganglion cells (Fig. 43). In the cells coarser neurofibrillae run through the cell-body from one process to another, and inside the cell-body these are everywhere connected by a number of finer fibrillae forming a distinct network (Figs. 43 and 44). The processes leave the cell-body in every direction, and the neurofibrillar network of the cell-body is continuous with that of the processes. In short, these multipolar cells possess every feature of true nervous elements, and it seems to me that there cannot be the slightest doubt but that we have to do here with real multipolar nerve-cells of the same character as the sympathetic nerve-cells of the vertebrates.

In most cases no difference was discernible between dendrites and neurites, the processes of the cells being all of the same structure and pattern. These ganglion cells are very numerous and are distributed very regularly in a thin layer on the wall of the liver, caecum, the oesophagus, and the post-hepatic middle intestine. They form a regular plexus, the cell processes extending in the thin sheath covering the wall in every direction, but always in the same horizontal plane. They intertwine to form plexiform bundles, as shown in Figs. 42-4. As far as could be gathered from study of the sections, with the exception of a few rare cases the processes of these multipolar cells anastomose freely with each other.

With regard to these anastomoses we have to distinguish between the processes of the different cells (Fig. 45) and the connexion of the cell processes with the coarser nerve-fibres running in bundles between the ganglion cells, thus building up the enteric plexus itself. We find synaptic connexions everywhere between the cell processes and the coarser nerve-fibres running between the cells, the post-ganglionic fibres (see fig. 46). These synaptic junctions present all the

features of true syncytial connexions, and strongly resemble the pictures given by Bozler (1927, 1928) of the connexions and synaptic junctions between the

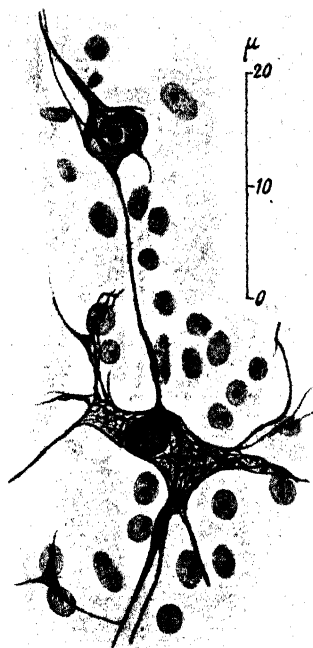


FIG. 45. Two anastomosing ganglion cells, enteric plexus of adult *Amphioxus*.

nerve elements in *Rhizostoma* and by Young (1933) of the synaptic connexions between the sympathetic cells and the post-ganglionic fibres in the Selachians.

In this way these ganglion cells of the enteric plexus of *Amphioxus* are comparable with the 'single nerve cells' Young described in the post-branchial nervous plexus of *Scyllium canicula*, which are also devoid of capsules and found at nodes in the post-branchial



network and whose dendrites make contact with neighbouring fibres without the latter terminating (see

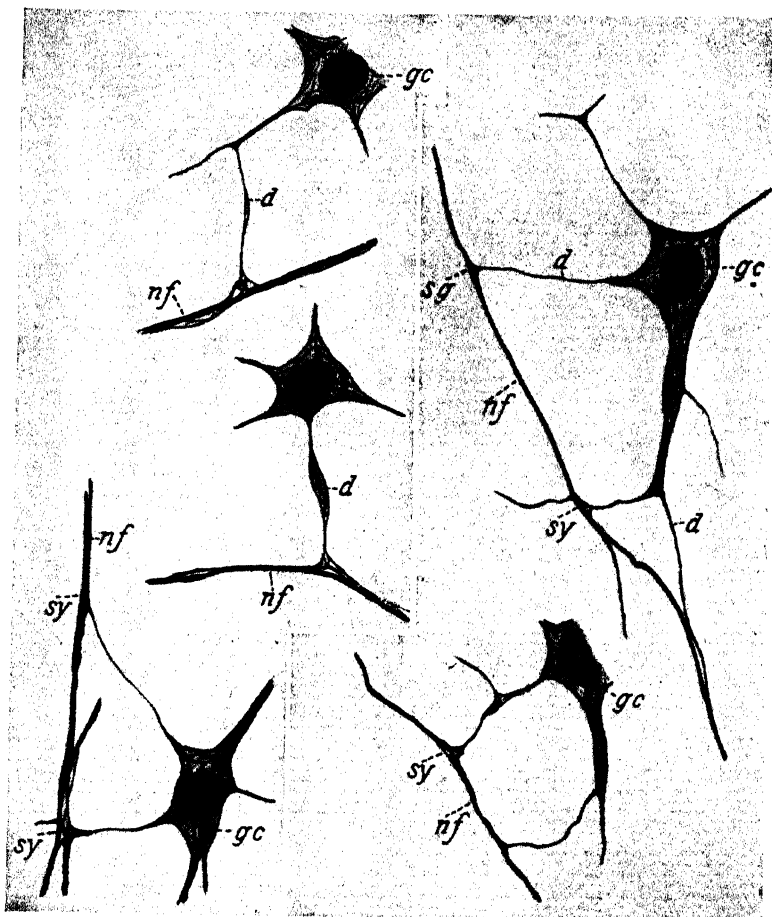


FIG. 46. Synapses between the processes of sympathetic ganglion cells and nerve-fibres in the post-branchial plexus of adult *Amphioxus*. After Boeke.

Fig. 48, after Young). They are also comparable, on the other hand, with the primitive ganglion cells in the nervous system of lower invertebrates, as described by Bozler, Sanchez, Patten, Carlson, and others. Even

coarser anastomoses between different ganglion cells are present (Fig. 45), of the same character as the cell-anastomoses described and pictured so beautifully by Apathy in *Pontobdella* forty years ago, but these coarser anastomoses are not to be compared with the true synaptic junctions mentioned above.

These synaptic junctions could be studied in the enteric plexus of *Amphioxus* using thin sections under the highest powers of the microscope (Fig. 46), and I am convinced that here we have to do with a true syncytial synaptic junction, a real continuity of living substance, and especially of neurofibrillar substance, even when the staining of the two parts of the synapse is a little different.

These ganglion cells are never enclosed in capsules, nor do they lie in groups like the encapsulated sympathetic cells of the vertebrates; they are always found lying at the nodes of the network formed by the post-branchial nerve-fibres. Even their synaptic junctions are protoplasmic and continuous. The same fact is described for the sympathetic ganglion cells of *Petromyzon* by Sakusseff in 1911.

In *Amphioxus* a true sympathetic chain (sympathetic trunk) is entirely absent, and in this connexion may be mentioned the fact that according to the investigations of Young (1933) even in Selachians there are no long pre- or post-ganglionic pathways in the sympathetic nervous system and therefore no true sympathetic chains, though the ganglia of adjoining segments are sometimes connected (cf. Chevrel, 1887; Botazzi, 1902).

*Part IV.* The last point to be settled is, whether one is entitled to compare these ganglion cells of *Amphioxus* with the ganglion cells of the enteric plexus of the higher vertebrates. What is the nature of the stellate ganglion cells composing the enteric plexus of

*Amphioxus*? With what elements are they to be compared? In order to discuss this question it must first be emphasized that they lie everywhere in a syncytial arrangement. In the second place it has to be borne in mind that they lie at the nodes of the plexus exactly like the sympathetic cells of *Petromyzon* (Sakusseff, van Wijhe) and the 'single cells' of the Selachians (see Fig. 48), as pictured by Young (1933).

They are not enclosed in capsules like the larger ganglion cells of the Selachian sympathetic plexus or the plexus of Auerbach of the higher vertebrates. In this they strikingly resemble the interstitial elements, and, in fact, the more one studies these sympathetic cells of *Amphioxus*, the more it seems that they are primarily comparable with the interstitial cells described above.

When one compares these ganglion cells with the interstitial cells of the higher vertebrates, one may ask, what is the real value of this comparison? In what manner is the enteric plexus of *Amphioxus* comparable with the enteric sympathetic plexus of the higher vertebrates? What position do these anastomosing non-encapsuled cells in *Amphioxus* and the interstitial cells of the enteric sympathetic plexus occupy in the economy of the animals concerned?

In the two points mentioned above the sympathetic cells of *Amphioxus* strikingly resemble the neuroblasts in a tissue culture (Mossa and Levi, Lawrentjew and Grigorieff, 1932, and Boeke, 1937). In the pictures given by Grigorieff (1932) we see the neurofibrillar structure of the neuroblasts and the anastomosing of their shorter processes (cf. Lawrentjew, 1932), whilst their longer cell-processes are seen growing out freely into the culture fluid (Fig. 47). Such pictures are very common, and indeed the resemblance to the pictures of the anastomoses of the ganglion cells of the enteric

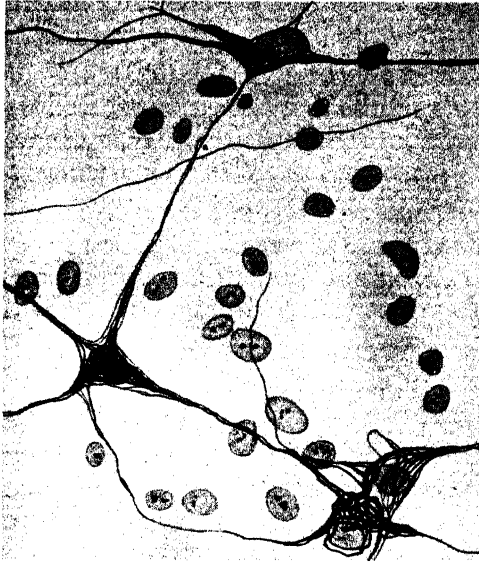


FIG. 47. Three anastomosing ganglion cells in a culture *in vitro* of a piece of the brain of a 7-day chick embryo. Culture of 72 hours. After Grigorieff, 1932.

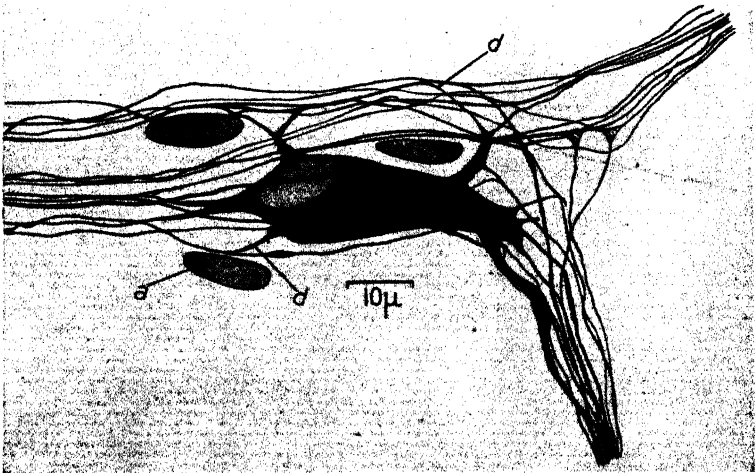


FIG. 48. 'Single ganglion cell' in enteric plexus of *Scyllium canicula*. After Young, 1933.

plexus of *Amphioxus* is very striking. This similarity in my opinion is not a mere superficial resemblance, but has a deeper meaning. When one studies figures given by Stoehr of the anastomosing Schwann-cells of the enteric plexus, for instance (Fig. 7, 1934), in which two Schwann-cells from the nervous plexus in the wall of the stomach of a young child are shown, one notices here also an entirely syncytial arrangement of the elements in question. When these figures are compared with those mentioned above, it is interesting to note the conformity of the general character of their structures. It seems very probable that what Stoehr has depicted here are nothing more than syncytial 'interstitial cells', the old interstitial neurones, *neurones sympathiques interstitiels* of Cajal, the place where the nervous impulse is transformed, the *Umwertungsstellen der Erregung*.

An attempt has been made to demonstrate that these interstitial elements are to be regarded as true interstitial parts of the sympathetic end-formation, and that from them arises the so-called intra-protoplasmic periterminal network, by which the nervous impulse is transmitted to the various organs of response. They are of the same nature as the elements in the core of many sensory corpuscles, such as tactile cells, and perhaps similar to the small ganglion cells described by Leontowitch in the walls of the arteries, and by Bethe in the connective tissue of the frog's mouth.

One is then entitled to say that there is no fundamental difference between the syncytial elements of the end-formation of the sympathetic plexuses which conduct the nervous impulses, and the elements carrying the impulse to or from the different end-organs. This whole end-formation has to be regarded as a syncytial arrangement which brings the terminal formation into protoplasmic connexion with the

neurofibrillar strands and with the organ of response. The conclusion, then, has to be drawn that the end-formations of the nervous sympathetic pathway, the so-called 'interstitial cells', are in protoplasmic continuity with the ganglion cells at the beginning of this pathway.

Thus it seems that in order to arrive at a true interpretation of the ganglionic sympathetic plexus of *Amphioxus* and of the higher vertebrates, we must give up the classical and traditional distinction between nerve elements and mere conducting elements, and that it must be acknowledged that intermediate elements may exist between them.

In this way one might compare the interstitial elements of the sympathetic end-formation with primitive ganglion cells, as already suggested by Cajal, when he called them *neurones sympathiques interstitiels* and attributed to them the faculty of giving off impulses to the end-organs, 'perhaps under the influence of the sympathetic plexus' (Cajal, 1911).

In the same way it would not be too bold to compare the interstitial neurones of Cajal and Lawrentjew with primitive ganglion cells such as we find in the nervous plexus of invertebrates (*Rhizostoma*, Bozler; *Astacus*, Alexandrowicz, a. o.) on to which in the course of evolution the larger encapsuled ganglion cells of the higher vertebrates have been superimposed. In this manner the results of the pharmacological experiments of Magnus and van Esveld, mentioned above, find a simple explanation. It is interesting that even in 1897 La Villa suggested the comparison of the interstitial cells of Cajal with the primitive ganglion cells of *Hydra*.

One might come, then, to the following conclusion: In the sympathetic nerve-plexus (ground-plexus) we may see a very old and very conservative nervous

system, which has preserved—speaking phylogenetically—many and primitive characters. From it the encapsulated larger cellular nervous elements of the sympathetic plexuses of the higher vertebrates have differentiated. It is very probable that the cellular elements of the enteric plexus of *Amphioxus* and of the nervous plexus in the mammalian and human iris are primitive in nature, and comparable to the cellular elements of the nerve-net of lower invertebrates. They are probable primitive elements which one sees preserved in the sympathetic plexus of the higher vertebrates as ‘interstitial cells’ and as non-encapsuled cells in the plexus of *Petromyzon* and the *Selachians*. They can be compared with neuroblasts as they develop in cultures *in vitro* (Grigorieff and Mossa), which here are seen to be regaining their true character. Seen in this light the similarity between the figures mentioned above would acquire a deeper meaning than a mere likeness in form. In it would be revealed a fact of phylogenetic importance. One would be able to understand better the beginning and evolution of the sympathetic nervous system in the various classes of invertebrates. The development of the sympathetic plexus in *Amphioxus* would not remain an isolated fact, but would become comprehensible as a stage intermediate between invertebrates and vertebrates, on to which the larger sympathetic cells of the higher vertebrates have been superimposed in the course of evolution as controlling elements.

One would understand better the so-called ‘interstitial cells’ and their peculiar character in the sympathetic plexuses of the higher vertebrates, the elements of the ground-plexus surrounding striated muscle-fibres and so on.

The unsolved riddle of the cells of the core of the sensory corpuscles, the tactile cells, the elements

surrounding and carrying the terminal arborization of so many different sensory corpuscles, would perhaps find a solution. These too may perhaps be regarded as interstitial elements, intermediate elements between the conducting nerve elements and the elements receiving sensory excitations.



## CHAPTER IV

### ON THE PRESENT STATE OF THE NEURONE DOCTRINE AND OF OUR KNOWLEDGE OF THE SYNAPTIC JUNCTIONS BETWEEN NERVE-CELLS THEMSELVES AND BETWEEN NERVE-CELLS AND END-ORGANS.<sup>1</sup>

THE question of the structure of the synaptic junctions between neurones and between nerve-fibres and the end-organs innervated by them is essentially a physiological question. It is the place where the nervous elements come into physiological relation with each other, that is, where the impulse is passed from one nerve-cell to another or where nerve elements come into relation with other cellular elements or to an end-organ. It is, however, undoubtedly right to look at it from a morphological standpoint also; for however valuable the physiological observations may be, as long as their real histological basis is disproportionately small or entirely missing, even the best-founded physiological theories remain nebulous. Histology still remains the basis for all our physiological deductions and theories, even when we acknowledge that histology has altered greatly in the course of the last fifty years, and that our present histological methods seem quite inadequate to resolve this question in a convincing way. We are also unfortunately restricted to studying synaptic junctions histologically in fixed and stained tissues, that is to say, in tissues put to death by strong chemical fixatives.

Our knowledge of the exact nature of the physiological process of nervous transmission is far too small to enable us to work out the structure of the different synaptic junctions by physiological observations alone.

<sup>1</sup> Rewritten after a paper read before the Anatomische Gesellschaft in Königsberg, September 1937.

The histological facts elucidated in different aspects of the structure of nervous end-formations are so numerous, that histology has a right to be regarded even in its present state as the indispensable basis for physiological convictions and theories.

It is obvious that in a review like this an impersonal and neutral treatment of the subject cannot be expected. The problem is far too fundamental in importance and the time available for discussion too short for me to do much more than bring my personal convictions to the fore and give a personal note to the description of facts described by others. I will try to do it in as objective a manner as possible; nevertheless, my personal opinions will obtrude and thus necessarily distinctly colour the whole subject, as was the case in preceding chapters. This mode of treatment should not be criticized too severely, especially in the present case, for a purely neutral descriptive account of such a subject is what is looked for in a collection of abstracts and not in a monograph such as this. Here the reader expects personal treatment of the subject based upon personal research and criticism. The only stipulation is that it must be thoroughly honest.

A review of the neurone theory. One must ask at the outset whether the old point of contention, continuity versus contact, conceived and brought up in the previous century, nourished on the old conceptions of the mosaic doctrine, which regarded the cells merely as bricks, and fed, so to speak, on cement substance, *Kittsubstanz*, has not now entirely lost its former importance.

We suggest that the theory should now be replaced by a new set of problems. What is the nature and the structure of synaptic junctions consisting of living substance? The synapses bring the different neuronic elements into relation; they are the places where the

nervous impulse is passed over from one nerve-cell to another or to end-organs ; positions which have to be regarded as being of different structural organization, *Umwertungsstellen der Erregung*, places where the impulse is transformed.

The question of the future will be, whether these synaptic junctions are really of different structure, or whether there is unimpeded continuity of protoplasm, a *Terminalreticulum* as described by Stoehr, between the neuron elements and their end-organs. Is there everywhere protoplasmic continuity at synaptic junctions, or are they composed of inert, lifeless material of a colloidal nature ?

The burning question of the day is not the old one of continuity versus contact, but it is the question of the nature, physiological and histological, of synaptic junctions (*die Synaptologie*, Lawrentjew, 1936), their structure and their physiological properties.

This question of the structure and the physiological properties of synaptic junctions is no longer intimately connected with the old contention : continuity versus contact, but with modern problems of the connexions of cellular elements in a multicellular organism, of the 'totality' of the organism, of the plasticity of the nervous system and the way it is influenced during development by an organizer, by its surroundings, by specific hormones, &c. It has to take into consideration, much more than did the old adages of the previous century, modern ideas concerning the conduction of nervous impulses in living tissues, concerning the polarizing effect of the reflex arc (or the synapse) on the conduction of these impulses, concerning the alterations of this conduction of the nervous impulse when passing living or inert barriers, and concerning the humoral changes in living tissues produced by the nervous impulse which innervates them.

To make my meaning clearer I shall discuss the question of synaptic junctions from a more general historical standpoint. The term 'synapse' was introduced by Sherrington and Foster in 1897 to denote the nexus between neurone and neurone in the central nervous system, especially in the reflex arc, and has been extended by many authors to include the connexion between the nerve-endings and the elements of the body they innervate, the contractile muscular elements, the glands, the sensory elements, tactile cells, &c. The term 'synapse' had primarily a physiological meaning, as worked out by Sherrington. In the synapse, as mentioned already, the stimulus is altered, the phenomenon of fatigue through reflex arcs is more marked than in the nerve-fibre, there is often a delay in the transmission in the reflex arc, which is referable to transmission through the synapse. Many drugs act especially on the synapse, such as curare, nicotine, &c. In the synapse the conduction of the stimulus is polarized, that is, made irreversible, and thus the physiological meaning of the synapse is quite clear. It points unmistakably to an independent nature (in a physiological sense) of neurones. To the physiologist, the independence of the neurones is a definite and almost undisputed reality. In this sense one has to admit that the neuronists have been nearer to the truth than the antineuronists of the old school, because they have recognized, in essence, that there is a difference between the 'contiguity' between two neurones and a full and unmitigated continuity of neuroplasm between two neurones. But here one must be careful not to confuse this physiological independence with an anatomical independence in the sense of the old neurone theory. There is room even in physiology and in clinical neurology for different opinions. Thus one of the most distinguished neurologists in Germany writes that, in

his opinion, the reticulate structure of the nervous substance is the most suitable for giving a sound basis for the understanding of the physiology of the nervous system. In such a structure there seems to be no place for the conception of the synapse, and in this way it is incompatible with the neurone theory.

It seems to me, and here I am sure that most neurologists will agree, that a synaptic junction between two neurones, a place where the impulse may be altered or even prevented from passing on, *eine Umwertungsstelle der Erregung* as I have called it, is of fundamental importance and certainly more helpful in enabling us to understand the physiology of nervous tissue than is the conception of a complete and unmitigated continuity of neuroplasm without any place of transition between the two elements, as the old school of anti-neuronists would have it. There must be some compromise here and the problem must be renamed and redefined even in physiology. The real difficulties lie in the classical anatomical neurone theory. The physiological conception of the synapse must of course have a sound histological basis; Sherrington describes it in the following manner, which I wish to quote somewhat extensively, as it gives such a clear expression of his opinion as well as the current opinion amongst histologists and neurologists :

‘As to the existence or non-existence of a surface of separation or membrane between neurone and neurone, that is a structural question, on which histology might be competent to give valuable information. In certain cases, especially in Invertebrata, observation indicates that many nerve cells are actually continuous one with another. It is noteworthy that in several of these cases the irreversibility of direction of conduction which is characteristic of spinal reflex arcs is not demonstrable; thus the nerve-net in some cases, e.g. Medusa, exhibits reversible conduction. But in the neurone-chains of

the grey-centred system of vertebrates, histology on the whole furnishes evidence that a surface of separation does exist between neurone and neurone. And the evidence of Wallerian secondary degeneration is clear in showing that that process observes strictly a boundary between neurone and neurone and does not transgress it. It seems therefore likely that the nexus between neurone and neurone in the reflex arc, at least in the spinal arc of the vertebrate, involves a surface of separation between neurone and neurone; and this as a transverse membrane across the conductor must be an important element in intercellular conduction. The characters distinguishing reflex-arc conduction from nerve-trunk conduction may therefore be largely due to intercellular barriers, delicate transverse membranes, in the former.' (Sherrington, *The Integrative Action of the Nervous System*, p. 18.)

'As there is evidence that similar features, though not usually in such marked extent, characterise conduction from efferent nerve fibre to efferent organ, e.g. in nerve-muscle preparation, in nerve-electric-organ preparation, here too the change may well be referable to the surface of separation admittedly existent between efferent neurone and effector cell.' (l.c., p. 16.)

'Even should a membrane visible to the microscope not appear, the mere fact of non-confluence of the conductive element of one cell with the conductive part of the other implies the existence of a surface of separation. Such a membrane would be a mechanism where nervous conduction, especially if predominantly physical in nature, might have grafted upon it characters just as those differentiating reflex-arc conduction from nerve-trunk conduction. For instance, change from reversibility of direction of conduction to irreversibility might be referable to the membrane possessing irreciprocal permeability.' (l.c., p. 17.)

In this sense the physiological conception of a synapse is sound, and if the conductive element of the neurone be fluid, there must be a real surface of separation between the two fluid phases in the form of a substance constructed otherwise than the two

substances separated by it. For physiologists, even of the old school, this surface of separation is and remains living substance, but for morphologists (of the school of the former century), looking at the problem from the standpoint of the independence of the neurones, this nexus could only consist of dead matter, of cement substance. The real anatomical difficulty lies in the word 'membrane', which Sherrington quite correctly used only with a meaning of a 'surface of separation', but which was always interpreted histologically as a membranous intercellular barrier, and was therefore used as a corroborative and indisputable argument in favour of the classic neurone theory.

In this connexion it is of interest that in very special cases Young, Bartelmez, Bodian (1933, 1935, 1938) have described real membranes interposed between the neurofibrillae of the nerve-fibres ending on the cell and the cell itself. The neurofibrillar apparatus of the nerve-fibres and the cell are separated by the appearance of these membranes.

This seems to depend largely on the fixatives used. Even here they speak of a 'plasma membrane', indicating thereby that they regard it as consisting of living material, the *strato sinaptico* of Beccari. When reading these descriptions and looking at the beautiful drawings one is tempted to ask whether these special cases are true synapses in the common sense of the word as it is used here, and how it is possible that a nervous stimulus is transferred here. Of the physiology of these nervous junctions nothing is known. The anatomical structure of these 'membranes' is far from being settled definitely. The authors mentioned above use them as indisputable arguments in favour of the classical neurone theory, but it seems to me to be rather dangerous to generalize the findings, in such exceptional cases, of the physiology of which we know nothing at

all, and by their use to revert to the old ideas of the previous century.

Nowadays the problem has to be stated in a different way. It is obvious that the problem of synaptic junctions will be different in those cases where a connexion between two neurones is implied, also in those cases where the nervous impulse is passing from one histological element to another, to end-organs innervated by them, single muscle-fibres, gland cells, &c. According to many histologists, these connexions (the motor end-plates, for instance) are not synapses in the strict sense of the word. In the central nervous system the connexions between the different neurones will be far less complicated than in peripheral tissues: though here, too, there are more complicated aspects, for example, the exceptional case of the Mauthner cells mentioned above; the climbing fibres arborizing along the surface of the dendrites of the large Purkinje cells in the cerebellar cortex; the peripheral nervous plexuses of the sympathetic system with its problem of the interstitial cells all present many difficulties. As soon as the nerve-fibres reach their destination, as soon as they have to transfer the nervous stimulus to the different forms of innervated tissue elements, they have to adapt themselves to their new surroundings. The impulse must be liberated or taken up, and a series of new connexions has to be made: very close intimate connexions with other tissues which have been differentiated in order to bring the organism into close contact with the surrounding world and transmit to the central nervous system impulses which are often extremely delicate and finely adjusted. The nerve-fibres do not only come into contact with these end-formations, they become part of them, and they become harmoniously differentiated with the peripheral end-formations themselves. This seems to me to be possible



only when it is regarded as a differentiation in living protoplasmic substance, and not as passive formation of a lifeless inert material (*ciment unitif, Kittsubstanz*) involving mere contact without continuity of living alterable substance as the classical neurone theory would have it.

Thus it has been possible to demonstrate that in motor end-plates there is definite and obvious protoplasmic union between nerve-fibre and muscle-fibre. The same could be shown without any uncertainty in sensory corpuscles such as in the corpuscles of Meissner and of Grandry (Boeke, 1926, 1933).

According to Gerard, who has written an excellent paper on the correlation of structure and function of nervous tissues, from which the chapter on the physiology of the nerve-fibres and part of that on the synapse in Bloom's *Text-book of Histology* (1934) have been taken, 'these motor end-plates are not synapses in the true sense of the word, and yet, the phenomena of nervous conduction through them have been shown to be in many respects so similar to those of the true synapses that we are inclined to believe that, in general, physiologic features found in the one are probably present in the other also'. I agree entirely with him on this point, but when Gerard goes on to say (p. 211) 'that his condensed account of the peculiar physiologic features of synaptic junctions is based in part upon studies of motor end-plates, where the junctional tissue is visible, and in part upon those of true synapses in ganglia, where special junctional tissue is not evident or if present is very unlike that of motor end-plates', it seems to me that the real difference between these two is not of vital importance.

Thus, according to Gerard, one can speak of a synapse only when there is a visible structural difference between the protoplasm at the synaptic junction,

the 'junctional tissue' of Langley, and that of the cells which are there united. This is living substance, but not homogeneous with that of the two neurones which are connected by it. Even where a sort of membranous barrier is interposed at the synaptic junction, this is not inert material, but living substance, according to Gerard.<sup>1</sup> 'Protoplasmic continuity is the rule at synaptic junctions.' The synapses may be regarded as central adjustors of more varied and modifiable behaviour, particularly of greater learning capacity (cf. Boeke, 1929). But when Gerard then says that the physiological properties of the 'junctional tissue' of the motor end-plates are also unique, it seems to me that the difference is more in words than in histological features. It seems to me entirely justifiable to extend the notion of the synapse even as far as the connexions of the nervous terminal formations with the organs innervated by them, muscle-fibres or sensory corpuscles. One is then justified in saying that protoplasmic continuity is the rule at synaptic junctions, and that there is no inert barrier between the two elements (Gerard, p. 212). We then have to admit that the problem of synaptic junctions is different from the old conflict of the classical neurone theory, that is, contact versus continuity. The neurone theory has had its day and is obsolete, and we need a new descriptive term for the synaptical junction between the different nervous elements.

It is at this point that we must never forget that our knowledge of the histology of the nervous system is still very incomplete. To cite Cajal (1935, p. 937):

'wir müssen nie vergessen, daß unsere Kenntnisse vom Nervensystem noch mangelhaft sind, und daß der Leitgedanke des

<sup>1</sup> Even the membrane of the synapses on the Mauthner cells is described by Bodian (1937) as a plasma membrane, i.e. living substance.

Histologen ein weiser Skeptizismus sein muß, der, obwohl er die erworbenen sicheren Befunde nicht anzweifelt, sich doch nicht zu der Vorstellung verleiten läßt, daß eine Wissenschaft, die ihre Methoden nur vor 40 Jahren erwarb, schon den Schlüssel zum Aufbau des Nervensystems besitzt, dessen Aufklärung die größte Arbeit der Zukunft bleibt.'

To give a complete survey of the literature bearing on the subject of the neurone theory would be impossible here. It alone would require a book much larger than the present volume, and after all it would be quite unnecessary, for Cajal himself, the old and venerated founder and defender of the classical neurone doctrine based on the work of His, Waldeyer, and a host of distinguished histologists, has given us an excellent and very elaborate survey of the whole field of research in the *Textbook of Neurology* by Foerster and Blum published in the last year of his life (1936). All the arguments on which the old classical doctrine is based are treated and discussed by Cajal in the most perfect way, and it is hard to think that the revered veteran of our science, to whom we are indebted for so very much, has been compelled in the last year of his life to defend the neurone doctrine, the theory which he had devoted the whole of his scientific career to establishing.

The essence of the neurone doctrine from its inception until now is that the nervous system is composed of independent elements, the nerve-cells, which remain independent even in their mature form. According to Cajal the neurone doctrine is based on six maxims, which may be formulated in the following way (Cajal, 1936, p. 636):

1. *Anatomical individuality.* Every nerve-cell is an independent unit, separated from the adjoining elements, with which it is only connected indirectly, by contact. There are neither anastomoses nor fusions of substance whatever.

As one can see, this point is governed entirely and absolutely by the question of the synaptic junctions. If, says Gerard (1936), in any case there is complete fusion of homogeneous protoplasm between two nervous elements, then by definition this is not a synapse and the elements so connected are not neurones. But it seems to me, as soon as we admit the definition of the synapse given by Gerard, 'Protoplasmic continuity is the rule at synaptic junctions' (l.c., l. 212), as correct, that even in the case of a synaptic connexion between the nervous elements, provided we assume that it consists of living substance, the classical neurone doctrine collapses and has to be replaced by another formula, better adapted to modern histological ideas.

2. *Genetic individuality.* Every neurone together with all its processes, including the axon, has developed from a single embryonic cell or neuroblast, without any co-operation of other nervous or neurological elements. This development must remain from the very beginning independent of other elements.

3. *Functional individuality.* The neurone represents also a functional unity. The neurones are the only elements containing neuroplasm. Non-neuroplasmic substances are not able to take up or to conduct the nervous stimulus.

We shall have to discuss the neurone as a functional unit later, and also the point that only neurones are able to conduct nervous stimuli.

This is either tautology, or it means the death of the classical neurone doctrine. If neuroplasm only is able to transfer the nervous stimulus, it is impossible that there should be an inert colloidal substance ('ciment unitif, une substance granuleuse ou vacuolée', Cajal) between them, for by this the nervous impulse could not be transferred.

4. *Regenerative or trophic individuality.* After section of the axon, the cell-body of a neurone causes the regenerative outgrowth of the new axon (trophic influence). Autogenic regeneration does not exist.

5. *Unity of pathological mode of reaction.* When the physical or chemical integrity of a neurone is attacked it reacts independently of the other neurones, at least during the initial phases of the pathological process.

6. *The nervous stimulus is polarised.* Cajal's law of centripetal polarization of the neurone.

These six cardinal points upon which the neurone doctrine is based have been quoted from the latest paper by Cajal (1936) because in this paper, as he himself states, he has formulated his doctrine as clearly and lucidly as possible, and has brought his conclusions into better harmony with the new achievements of neurological research (l.c., p. 637).

It is clear that not all these points are of the same significance with regard to the neurone doctrine. Physiological individuality of nerve-cells may remain absolute, even though one has to abandon anatomical individuality. Indeed, physiological and functional segregation of the neuron elements is regarded by nearly all neurologists as the basis of every theory concerning the function of the nervous system, although here also a higher functional unit consisting of several neurones in more intimate connexion (a 'neural') is claimed by some (Schroeder). But even in a syncytium, physiological individuality may remain among the different elements which compose the syncytium as long as the intervening connecting substance, in case the synapse, is regarded as emphasizing different qualities of living protoplasm from the substance of the protoplasm of the elements connected by them.

In cardiac muscle, the different segments are separated by intercalated disks; they may show a separate functional activity, the contraction wave often ceasing in the sections at an intercalated disk. According to Lewis, in tissue cultures of cardiac myoblasts two cells without any trace of a cell-membrane and with the

smooth contractile fibrils continuing from one element into the other may show different rhythms of contraction. But even here they are regarded as forming a syncytium, and cardiac muscle may be taken as 'representing a syncytial, multinucleated mass of reticularly arranged protoplasmic bars in which contractile fibrils pass independently of cell territories' (most authors, according to Bloom). Everything depends upon a synaptic connexion by means of living substance with physiological properties differing from those of the two connected elements. Polarization of the nervous stimulus may thus be located in a synapse. This was most clearly pointed out by Sherrington many years ago when he formulated the idea of the synapse as a junction by living alterable protoplasmic substance. Polarization of the nervous impulse does not mean an interruption of conduction, as was supposed by De Castro, Lawrentjew, and others, but simply a transformation of its qualities, *eine Umwertungsstelle der Erregung*. This is only possible in an alterable living substance. Even when it is assumed that a specific hormone is formed in the synapse, be it acetylcholin, adrenalin, or sympathin, as has been so clearly demonstrated by Dale and Adrian and their followers, or if it be assumed that an electric double-layer is formed in the synapse (Leontowitch), or if it is assumed that in the synapse 'es sich handelt um eine biologische Schwingungserscheinung, die von elektrischen, chemischen, thermischen und kolloidalen Veränderungen begleitet wird' (Herzog, 1938), the basic question remains the same. In my opinion, whatever be assumed, an alterable living intermediate substance is undeniably needed in the synapse, not an inert colloidal membranous medium. As Bloom expressed it in his textbook (in the chapter written by Judson Herrick, 1934, p. 210): 'it should always be borne in mind, that the

surfaces which are thus in contact are living substance ; there is no inert barrier between the two elements.' Even the 'receptive substance' which Langley supposed to be present in the sarcoplasm of the motor end-plate must be living protoplasmic substance ; in the same way even the tonoplast in vegetable cells has to be regarded as composed of living, actively alterable material and not as an interface membrane of inert colloidal material. Even here we cannot regard the boundary-membrane as an inert barrier. And the same holds true for the curious membranous synapses described by Bartelmez and Bodian (1933, 1937) on the Mauthner cells of fishes, which were discussed on p. 93.

The value of Cajal's fourth point, that of the neurone as a regenerative or trophic unit, might be discussed at some length, and the result would be that the statement is not so unassailable as is generally supposed.

It is generally assumed that, after section of the axons of a peripheral nerve, Wallerian degeneration of the cut end sets in and the axis-cylinders of the peripheral stump of the cut nerve perish completely because they are cut off from their trophic centre, the perikaryon. It is further asserted that when regeneration sets in it begins as an outgrowth of the central cell-process, and proceeds from the central end of the stump into the peripheral degenerated portion of the nerve, thereby awakening it to new life. This, however, is still open to question, for even in the course of last year it was pointed out by the author in the *Textbook of Neurology* of Foerster and Blum that in nerve regeneration a co-operation between nerve-cells and the so-called lemnblasts in a syncytial arrangement must be assumed (Boeke, l.c., 1936). It was also pointed out that Cajal himself in his earlier writings described and figured this in his first descriptions of regenerative processes (Cajal, 1908, p. 33, fig. 5 ; Boeke, 1936, p. 1036). In

his later writings Cajal assumed a kind of symbiotic association between axis-cylinder and sheath-cells during regeneration. I must confess, however, that in reading his description of this symbiosis, one is reminded very strongly of the conceptions and descriptions of Held, which show a striking resemblance to the descriptions of Cajal. This is still more emphasized when one sees that even Cajal has to admit that during regeneration the outgrowing neurofibrillar cell-processes travel inside the protoplasm of the bands of Buengner. Hence his theory of a symbiotic association. Moreover, it was pointed out (Boeke, l.c., 1936 and 1930) that in nerve degeneration the axis-cylinder of the peripheral stump of a cut nerve-fibre does not perish entirely because it has been severed from its trophic centre, the cell-body on which it depends, as is usually assumed. It is pre-eminently the conducting mechanism, the neurofibrillar apparatus, which disappears and which may be restored to new life and new activity after regeneration has set in.

When the degeneration of peripheral nerve-endings which are large and distinctly visible, as, for instance, in the corpuscles of Grandry in the skin of the duck's bill, are studied as accurately as possible, we see that the tactile disk, which represents the end-ramification of the sensory nerve-fibre, does not perish immediately after the section of the nerve, but that it is only its neurofibrillar apparatus which disappears, and that the protoplasmic part of the tactile disk remains visible. Only after a time does this protoplasmic part of the tactile disk atrophy and disappear entirely, just as taste buds disappear, when the nerves innervating them are sectioned.

The degeneration process affects only the conducting mechanism, the neurofibrillar apparatus during its initial phase. Thus we can understand that in tissue



cultures, as Levi has shown, the axis-cylinder process of a neuroblast, when severed microscurgically from its trophic cell-centre, may remain alive and may fuse again with the new outgrowing cell-process of the same cell or of another cell without perishing. We must always bear this in mind, that the neurofibrillar apparatus of a nerve-fibre, however dark it may be stained or impregnated, does not represent the whole nerve-fibre, but that it is always surrounded by a thin layer of neuroplasm. These two substances together build up the nerve-fibre. In degeneration the conducting apparatus perishes; the neuroplasm fuses with the protoplasm of the lemnoblasts to form the bands of Buengner, and in regeneration the outgrowing regenerating neurofibrillar apparatus follows these conducting bands as fine fibrillar differentiations lying inside this protoplasm, as was described by Cajal himself.

To make my meaning clear I would emphasize that I am not attacking the usual description of the nerve regeneration process, but I am only trying to show that the fourth point enunciated by Cajal as one of the arguments in favour of the neurone theory is not so indubitably and securely settled as is assumed in most of the treatises and text-books which deal with this question. There are even here many problems of fundamental importance still unanswered. The details of the regeneration process, when outgrowing nerve-fibres are studied in preparations in which the surrounding elements also are stained, point far more strongly to a harmonious co-operation of all the elements necessary and indeed indispensable to the final result, the restoration of the harmonious function of the end-formations, than to a simple process of outgrowth of regenerating nerve-fibres.

The first two points only remain, which are of real conclusive value for the neurone theory in its classic

form; they are the anatomical and genetic individuality of the different neurones. When Bloom (1934, p. 208) says: 'If it should prove to be true, that there are instances where nerve cells are connected in a true syncytium, . . . then, by definition, these nerve cells are not neurons', it seems to me that it would be better to say: if it should prove to be true, that there exists an undeniable connexion by living substance between the neuronic elements, be it with different physiological properties, and that there exists in the end-formation either a constant fusing of the processes of the different nervous elements, or a transient ontogenetic syncytial phase, in which the formation of a true syncytium is interposed between the outgrowing of the original cell-processes of the neuroblasts and the formation of the definite and permanent end-organs; then the neurone theory is dead and both supporters and antagonists should look for another theory as a basis for renewed endeavours. Just as in every field of human energy at present the field of contention is changing, so it must be admitted that the classical conception of the neurone theory is obsolete, that one cannot fight further either for or against it, and that it is high time that it was buried together with so many of the old histological conceptions of the last century. Concerning the problems of the synapse, of the plasticity of the nervous system, of interstitial cells, of the sympathetic end-formation, and so many other problems, there is sufficient food for long years of strife and contention, even for the most militant.

Is it right to say that the neurone is the cellular unit of the nervous system, independent of the other cells and developed from a single embryological cell, the neuroblast, which retains its individuality, its cellular independence, through life? This is the question which is of fundamental importance. The problem of the

neurone theory is thus connected indissolubly with the general problem of the relations of the different cells in the multicellular body. It is exactly this problem which has now assumed quite another aspect to that which it had fifty years ago at the time of the conception and maturation of the classical neurone theory.

On this general problem I must restrict myself to a few remarks. That many of the observations upon which these conclusions are based have been made on material prepared by methods of silver impregnation, which are known to introduce artefacts which may obscure the true relations of tissue elements, and in which the neurofibrillar apparatus takes such a predominant stain, must constantly be kept in mind, and especially since American authors (Parker, Lewis, Matsumoto) have denied the existence of neurofibrillar differentiations in the living nervous elements, because in their opinion they were invisible in living nerve-fibres and cells even with the best dark-field illumination. Real neurofibrillae, however, have been seen, described, and photographed in living tissue cultures of nerve-cells independently by Weiss and Levi (1936), neurofibrillae which showed exactly the same features in the living cells and after the preparation had been fixed and impregnated. And the same thing can be seen in any series of tissue-culture preparations of the nervous elements of a chick-embryo (cf. Lawrentjew, Grigorieff, and others). Thus the existence of neurofibrillar differentiations in living nerve-cells is indisputable. The observations of both Weiss and Levi, that the neurofibrillar structure is variable in life during the growth of the nerve-cells in the tissue cultures, and that the neurofibrillae are plastic, as has been insisted upon by many previous authors (cf. Boeke, 1926, 1929), seem to be of value in this connexion.

I still maintain the same point of view as I did in

1926 as to the general side of the question—that of the connexions of the cells in the organism, viz. that the old conception of the cell as an independent elementary organism has to be revised. The farther we penetrate into the wonderful organization of the cells in the multicellular body and into their differentiations, the cell itself appears to lose part of its independence as an elementary organism. Many of them are seen to lose their boundaries in the course of development and fusing together to form a syncytium, which may be disintegrated again into cellular elements. Everywhere one gets the impression that the cell-lineage of the cellular elements of the full-grown body is by no means clear in most cases. The old cell-theory which regarded the cells as self-supporting, as independent self-sustaining units, as bricks building up the organism, as a mosaic connected only by a ‘sticky substance’ on inert material, cannot be maintained, and has to be revised. We are in danger of being lead astray by this theory, and in the light of more modern thought on continuity in nature the old conceptions of the classical cell-theory are out of place.

The nineteenth century was a time of analysis as a basis of all investigations, an analysis which always attempted to dissect every living thing into its elements, to unravel it and to reduce the phenomena of life in the organism to a few independent factors: as if it would be possible to explain in this way the coherence and continuity of the phenomena of life in the organism and the wonderful harmony of the living organism in its totality. The organism is not a conglomerate of cells, a colony of elementary organisms. Certainly the analytical method is still needed to make the details of a physiological process clear which are often bewilderingly complex. But in the former century analysis, as the only reliable method, and above all as

a doctrine of the only possible way to explore or to understand the phenomena of life in nature, did form the basis of every investigation. And we are proud to state that in this way it came to a definite and final end. We are everywhere struck with the exquisite harmony of the living organism, a harmony between the different tissue elements which demonstrates the domination of the individual over the elements which compose it—the cells. The conception of a struggle for life of the cells in the organism, worked out by Roux years ago to form the basis of his theory of functional adaptation as an analogy to the idea of a struggle for life in nature, cannot be true, because it does not sufficiently take into account this harmony within the organism, to which every apparent struggle is subjugated.

In nature, the individual itself is fighting for its life and for the maintenance of its species. In this fight every individual is endeavouring to destroy remorselessly everything that is weaker, and only the fittest survive in the struggle. What is called the harmony of nature is founded on our own artistic view of the things around us, and when we speak of harmony and unity in nature either we unconsciously transfer the idea of the individual organism to the conception of the universe, or we feel behind the forces and phenomena of nature a Divine Power, before which we can only bow our heads in profound submission, without trying to explain it. Even here the struggle for life in nature is subjugated to the Divine Harmony, which governs nature as a whole.

But in the organism this harmony is a distinct reality. Every organism is a unity in itself, and the elements which compose it are in the first place a part of the whole, deriving their full value not from themselves, but from the individual to which they belong. The organism as a whole dominates the cells which compose

it. It blends them together, so to speak, subjugates them to form that unity of the living organism, that harmony of their organization, which is the greatest wonder and mystery of nature and fills us with such a profound admiration. We have analysed the organism, the body, into its cellular units. Now we have to search for functional units, for a living harmony. The entire body has been embedded in paraffin and cut into thin sections under a cover-glass. Now synthesis must build it up again to a *living whole*, a *living totality*.

It is true that in the adult organism, in which we have to study the finest details of the cellular units in order to get a clear view of their connexions, these details must be studied almost exclusively in fixed and stained material in which it is often exceedingly difficult to arrive at unimpeachable results; and it is true that many of the accounts of different authors who have tried to show that the cellular theory is wrong ('a myth', Dobell) have not been able to survive subsequent criticisms. Nevertheless, it seems to be an ascertained fact that even in the adult organism the cells everywhere lose their histological independence, that they are connected with each other, often building up a distinct syncytium, that even in the different forms of connective tissue they usually remain connected in the same way as during embryological development (Heringa, 1923). On the other hand, after a syncytial stage during development, as for instance in the development of smooth and striated muscle-fibres, they seem to re-form into distinct separate units. These units are better called 'functional units', for the cell-lineage of these newly formed so-called cellular elements of the full-grown body is by no means clear. The organism forms a continuum in which distinct 'cellular' units are often only visible when construction of the different organs is only possible by means of more or less distinct

constructive units, the cells of which could often be better called 'functional units' rather than 'histological cellular units'. If this conception is true, it is not to be wondered at that among the different parts of the organism it is the nervous system which must primarily exhibit phenomena in harmony with this view, in which this higher unit, the functional unit, plays a more dominant part. It is precisely here that Professor Schroeder, who read a report on the clinical side of the question under discussion here, laid so much stress on the urgency and necessity of using the term 'functional unit', the 'neural', as he calls it, for the groups of ganglion cells acting together and connected, physiologically and histologically, into a higher functional unit.

The neurone doctrine, with its sharp disjunction of the cellular elements of the nervous system, was based entirely on the cell-theory of the preceding century in its most absolute form; in this way it belonged to the mechanistic and analytic mental attitude of that time. The cell-theory, which analysed the organism into a host of independent separate elements, and which regarded the organism merely as a conglomerate, a colony of cells, a 'mosaic', was completely opposed to the interconnexion of nervous elements by means of living substance. The Golgi-method, which dominated histological study of the nervous elements almost completely, showed these independent elements with a clearness and a sharpness which seemed to leave no doubt whatever about their being separate, independent units. Experimental and embryological work (Harrison, Braus) seemed to support this view entirely and promote it to the rank of an unchallenged doctrine.

The last thirty years of our present century have witnessed a complete change in the face of science. Materialism of the former century has been left behind,

and we admit that living substance cannot be explained simply by laws governing the non-living world, and above all we have to admit that in the organism life goes far beyond the limits of cellular structures. We have had to acknowledge that the cells of the living organism are not the only living things in it and connected solely by a lifeless substance, the *Kittsubstanz*, and with lifeless ground-substance between them. This has nothing to do with the functional independence of the elements of the body. The organism is an harmonious unit in which the component elements are subjugated to the totality, to the whole of the organism. Why should it be necessary for the nervous elements which have to bring the different parts of the organism into an harmonious relation to be isolated anatomically from the other elements of the body, and to be separated everywhere from them by intercellular membranous barriers, or even remain at a distance from them as has been supposed by adherents to the classical neurone theory (Cajal and v. Lenhossek)? Do the corpuscles of Grandry lose their functional independence when protoplasmic connexions between the nervous disk and the two surrounding tactile cells are found? Does the cross-striated muscle-fibre lose its functional independence when it can be shown that it develops from a number of cells which fuse? Do the muscle-fibres of the heart-muscle lose their functional independence because they are united protoplasmically by means of intercalated disks (cf. p. 134)? Or do the motor nerve-endings on the muscle-fibres lose their functional independence when we show that they are embedded in the sarcoplasm of the muscle-fibre, and because here in this intermediate region we have to locate the 'receptive substance' of Langley, the synaptic periterminal network?

Is this hypolemmal position of the nervous end-



ramification only to be regarded, as Heidenhain contended, as an arrangement to attach the end-organ more strongly to the muscle-fibre (*Verankerung*) and to prevent it from being torn from the muscle-fibre during violent contraction? I do not think so. There is no stronger mode of attachment of one element to another imaginable than that of the end of the muscle-fibre to the tendon. And yet it is easy to demonstrate in most cases that the sarcolemma extends over the end of the fibre, that the collagenous tendon-fibrils do not pass over into the muscle-fibrils as has been maintained by Schultze, but are continuous with the reticular fibres on the surface of the sarcolemma. Why then should such a continuity between the nerve-ending and the muscle-fibre be needed merely to prevent the nervous end-plate from being torn from the muscle-fibre by its contraction? In my opinion this hypolemmal position is only another example of the insufficiency of the old cellular conception and an example of the continuity of the different cellular structures with each other, and is here of the utmost importance for the precise function of the motor end-organs, a true synapse.

However highly the Golgi-method is valued for its development of the knowledge of neurology, it has to be admitted that it has led one into dangerous paths with regard to the connexion of the nervous elements with each other. It is interesting to study the literature dealing with this question. In the older papers—for instance, from those of Cajal in the first years of his scientific career, of v. Lenhossek, and of the other past masters of the Golgi-method—we learn that the terminal arborizations of the axons remain at comparatively long distances from the ganglion cells with which they are in functional connexion. In the year 1895 v. Lenhossek states with absolute conviction 'die feinen

Endreiserchen, in die der Nervenfortsatz büschelartig zerfällt, laufen samt und sonders mit freien Spitzen aus; von einer Einmündung derselben in ein Netzwerk, wie sie Golgi vertrat, kann keine Rede sein. Die feinen baumförmigen Verästelungen . . . enden alle mit freien Spitzen. Dieser Nachweis lässt sich mit voller Sicherheit erbringen. . . .’ With the same absolute certainty Bethe and Holmgren maintained that absolute continuity existed. The Golgi-pictures, however, only showed the free endings drawn by v. Lenhossek.

Gradually, apparently under the influence of the more modern methods of investigation, in the pictures drawn by neuronists, we see how the free-ending nervous arborizations approach closer and closer to the surface of the ganglion cells to which they are related, until they come into contact with the surface and their expanded tips or ‘terminal feet’ appear closely pressed against the cell-body or dendrite. But even now the adherents of the classical neurone theory remain convinced that there is only cement substance, inert material, *Kittsubstanz*, *ciment unitif*, between the terminal feet and the cell-body, and Cajal in 1935, Windle and Clarke in 1928, Mihalik in 1935, adhere to their old convictions, although Bloom in 1934 warns us: ‘that it should always be borne in mind that the surfaces which are thus in contact are living substance; there is no inert barrier between them’ (Bloom, 1934, p. 210). As I mentioned before, we must always bear in mind that modern physiology everywhere locates the places of connexion of the different nervous elements, the places where the nervous stimulus is altered, where its physiological properties are changed, where humoral energy is produced, where the ‘receptive substance’ of Langley is found: in short, locates these places with their important physiological properties precisely in these synapses which are so well defined histologically. This

is only possible when we regard these synapses as consisting of living substance, as has been emphasized already at the beginning of this chapter, and exactly as has been insisted upon by Bloom. A synapse consisting of inert material, of *Kittsubstanz*, can only change passively, under the influence of the cell-body, not actively. If this is assumed, the interneuronic connexions regarded as consisting of inert material, the term 'synapse' loses its physiological significance and might better be replaced by a term of less precision and of a more general character. In a synapse built of living substance, in the modern sense of continuity, we may assume a bimolecular surface layer on the surface of the conducting substance, as Dale, Leontowitch, Herzog, Lillie, and others believe, and which was assumed years ago in the conducting elements, the neurofibrillae (Boeke, 1926, 1929). Thus a membranous barrier composed of living, alterable substance in the sense of the synaptic membrane of Sherrington, may be present without the necessity of assuming an inter-cellular histological membrane of inert material which a nervous stimulus could not pass without leading to its disintegration. 'Even the hypothetical synaptic membrane of Sherrington must be an arrangement of units of the living substance, and this arrangement may be present in the periterminal network, not as a real visible membrane, but as a biphasic condition of the living substance itself' (Boeke, 1929, p. 689).

That a synapse between ganglion cells may be built entirely of living substance with protoplasmic continuity, but with different staining qualities, is to be seen in the sympathetic ganglion cells covering the wall of the gut of *Amphioxus lanceolatus*, which according to Dogiel, who described them in the walls of the branchial bars, lie in the nodal points of the enteric nerve-plexus, and which form a true continuum with

protoplasmic synaptic junctions between the cells and the nerve-fibres of the plexus (Boeke, 1935, 1937). In Figs. 43 and 44 some of these cells are pictured. They were described at some length and compared with the so-called interstitial cells of the higher vertebrates in the third chapter.<sup>1</sup> It was also stated there that anastomoses of neuroblasts are clearly to be seen in tissue cultures of nervous elements (Grigorieff, Lawrentjew) (Fig. 47), exactly as had been described years ago by Apathy in the tissues of *Hirudinea*.

It is not necessary that these synaptic junctions should have the form of minute rings or net-like endings everywhere such as were described so convincingly by Lawrentjew in 1935. They may be in the form of larger net-like expansions of the neurofibrillar structure or of what I have called *wirksame Strecke*, long-drawn-out junctional tissue. Perhaps the connexions of the dendrites of the so-called climbing fibres of the Purkinje cells of the cerebellum (Tiegs) are of this type. The same *wirksame Strecke* of protracted junctional tissue are found in the sensory corpuscles with often bewilderingly complicated neurofibrillar convolutions, such as in the corpuscles of Meissner, the end-bulbs of Krause, the corpuscles of Ruffini, &c. (Fig. 35). But even here a synaptic junction is needed, let us say a synaptic field, a stretch of neurofibrillar tissue where the stimulus is altered, *eine Umwertungsstelle der Erregung*, as was discussed at some length at the beginning of the third chapter (p. 98 of this volume). Also in the end-formation of the sympathetic system with its poorly localized reactions, and its more general and protracted movements, it seems difficult to understand how such minute ring-like endings could produce such general reactions. As Professor Petersen wrote me: 'besonders beim sympathischen Grundplexus, wo die

<sup>1</sup> pp. 109-13 of this volume, third chapter, on the 'interstitial cells'.

Erregung und die Reaktion doch mehr diffus erscheint, nicht so sehr auf die einzelnen angeschlossenen histologischen Elemente beschränkt, brauchen wir doch nach den neueren Auffassungen ein chemisches Zwischenglied'; here it seems to me, a protracted stretch of junctional tissue is more appropriate than such minute ring-like endings, lying here and there on the tissue elements. Even here we need a synaptic junctional tissue and not an undifferentiated terminal reticulum (Stoehr) which never ends, and in which all the nerves (sympathetic, vagus, according to Reiser even spinal somatic nerves) are intermixed to form a veil-like inextricable mass of net-like or sponge-like tissue, enveloping every element of the body, preventing every possible physiological endeavour at disentanglement. In the sensory corpuscles mentioned above and in the system of the interstitial cells discussed in the course of the third chapter, we find examples of a true lengthened-out synaptic junction, a true *wirksame Strecke*.

Cajal's conception of the genetic individuality of the neurone (see p. 133), the development of the neurone from a single embryonic element or neuroblast, implies that it must from the beginning remain independent of other elements. Here one might mention firstly the description of Held in his monograph for the year 1909, in which he mentions a syncytial stage in the very young neuroblasts before they develop into distinct separate ganglion cells of the adult type, and secondly the more modern description by Grigorieff (1932) and Bauer (1935) of anastomosing ganglion cells in tissue cultures of young chick nervous tissue.

But even when we turn our attention to the later development of the motor nerves we see that a distinct syncytial stage of the nerve-fibres in the region of the developing muscles innervated by them occurs between

the first growing out and the definitive development of the motor end-plates, as has already been mentioned in the third chapter (see Figs. 37 and 38). In the short muscle-fibres of the tongue of small animals (Fig. 37, tongue of a mole embryo) this syncytial stage is distinctly seen, and even in young animals (Fig. 38, from the tongue of a new-born mouse) motor end-plates are often seen lying at the end of several fibres which together build them up. From these the definite end-plates are formed (Fig. 39, tongue of a young mouse, Boeke, 1927). This syncytial intermediate stage may be seen everywhere, and in the striated muscle-fibres of the ciliary body in birds this plexiform innervation by a network of syncytial neurofibrillar strands (Fig. 36) may be followed step by step into the individual innervation of each separate muscle-fibre by a single independent end-plate, exactly as in the tongue of young mice or moles. Cajal himself years ago described these curious forms of young motor end-plates, but he considered them as *erreurs évolutives*. Even convinced adherents of the classical neurone theory have to admit this intermediate syncytial stage in the development of the motor endings, for instance Schimert.<sup>1</sup>

It is obvious that if such a syncytial stage is a reality, Cajal's second thesis in support of the classical neurone theory falls to the ground. Furthermore, according to the investigations of Dogiel, Heringa, Dijkstra, and others, the same holds true for the development of different sensory corpuscles. Here, also, we find an intermediate syncytial stage in the development of the end-corpuscles, and we find the same in cases of regeneration, as was pointed out so clearly by Dijkstra for the regenerating corpuscles of Grandry in the skin of the bill of ducks and geese. Even in adult nervous end-formations we often find a net-like struc-

<sup>1</sup> Verbal communication.

ture which is entirely incompatible with the classical neurone theory. As has been described at some length in the second chapter of this volume, we find a distinct net-like nervous plexus in the layers of connective tissue covering the eye-ball. Here the sympathetic ground-plexuses can be seen very clearly, and it is easy to trace its origin from the thicker nerve-bundles, and to follow the course of its strands through the connective tissue even in thin tangential sections through the sclera and choroid because they are stretched out in the same plane. They are following the blood-vessels, accompanying the blood capillaries, or running free through the connective tissue. From the thicker bundles of the ground-plexus spring thinner and thinner strands, until the neurofibrillar strands are only composed of a few separate loose varicose nervous threads, which can be seen so clearly in well impregnated sections (Figs. 24, 25). In these preparations every single neurofibrillar thread is visible. Here the existence of real net-like structures is indubitable, quite apart from any artificial malformation caused by the fixing agent (formalin). Even in sections in which the thicker neurofibrillar strands are seen as non-varicose smooth threads running seemingly independently of each other, closer examination reveals the exceedingly delicate anastomosing varicose fibres of the ground-plexus with astonishing clearness, which leaves no doubt about their forming a real net-like formation. In methylene blue preparations the same reticular sympathetic nervous plexus is plainly visible (cf. Leeuwe). Histologically a reticular structure of the sympathetic ground-plexus seems to be beyond any doubt. One may ask whether the results of the degeneration experiments of Lawrentjew, Kolossow, and Schimert, who found degenerating nerve-strands in the sympathetic plexus of the wall of blood-vessels

after cutting some of the sympathetic nerves, do not directly contradict the possibility of the existence of a net-like structure of the ground-plexus. On the grounds of their experiments, the authors themselves positively deny the existence of a reticular sympathetic plexus. But firstly, the droplets of the degenerating axis-cylinders were to be seen chiefly in the thicker nerve-bundles where neurofibrillae may still be running separately, and secondly, what do we know of the conducting process of the stimulus and about the course of the degenerative process setting in after the cutting of some of the strands in and through a reticular plexus in which the different neurofibrillar strands are so obviously anastomosing with each other? We do not yet know anything about the course of the degenerating process in the loose reticular strands of the sympathetic ground-plexus, nor about its course in the sensory ground-net which Stefanelli demonstrated in the connective tissue of the skin. Thus the results of the degeneration experiments mentioned above do not seem to give a conclusive reply to the question of the reticular structure of the ground-plexus. Then we have to consider a second point. Of course it is true that, especially after fixation with formalin, artificial glueing together of seemingly independent neurofibrillae may occur, but this is only possible when these neurofibrillae are embedded inside the same protoplasmic sheath, and not when they are separated by cellular sheaths of Schwann. Nageotte calls these *fibres nerveuses composées*, and it is especially inside the sympathetic ground-plexus that the neurofibrillar strands are running syncytially inside the same protoplasmic sheath (*Protoplasmastränge* of Stoeckh and Reiser). Where this is the case, the independence of the individual neurofibrillae is in my opinion only of minor importance; we do not even know whether we have to



do there with permanent or more or less transient neurofibrillar structures. We know that neurofibrillar structures are *plastic*. The problem of the conduction and transmission of the nervous stimulus through the ground-plexus with a net-like structure and with anastomosing neurofibrillae running inside a syncytial sheath-arrangement, and the question whether function itself has any influence on the *plastic* neurofibrillar structures with which we have to do in the sympathetic end-formation with its syncytial arrangement of neurofibrillar strands, is still open, and has not even been studied. Viewed in this light it seems premature and wholly unjustifiable to draw conclusions about the independence of the neurofibrillar structure of the sympathetic neurones from degeneration experiments such as those of Lawrentjew and Schimert. For the morphological evidence of a net-like structure of the sympathetic end-plexus is too conclusive, and, it seems to me, too much in harmony with modern physiological conceptions and ideas to be lightly set aside.

Of still more importance with regard to the question of the intimate structure and connexions of the different neurones is the problem of the interstitial cells, which has been discussed at length in the course of this monograph, especially in the third chapter. As demonstrated there, even Cajal himself had to admit that these interstitial elements freely anastomose with each other, that they form a syncytium, and that they are connected with the elements of the enteric plexuses of Auerbach and Meissner. As I tried to demonstrate, they are found as intermediate elements at the end of the sympathetic end-formation and they are of the highest importance for the transmission of the nervous stimulus. I might add here that Tinel, the French neurologist, in his admirable text-book of neurology (*Le Système nerveux végétatif*, Paris, 1938) came to the

same conclusion and demonstrates the high importance of these elements. It would be superfluous to discuss the problem of these interstitial cells here again after having discussed them at length in the foregoing chapters. Here I would only call attention to this problem, because of its importance for our conception of the physiological function of the sympathetic end-formation, and because the interstitial elements in their syncytial arrangement form a conclusive argument against the adequacy and the truth of the classical neurone doctrine. They show how little we know as yet of the minute structure of the sympathetic end-formation, how difficult and how complicated are the problems attached to the study of the physiology of this nervous formation, and how dangerous it is to adhere to the simple classical conceptions of a theory conceived and grown to maturity during the last decades of the foregoing century together with the classical doctrine of the independence of the cellular elements in its most concrete and unmitigated form.

To conclude: the advancement of neurology owes more to the classical neurone theory than to the doctrine of full continuity of the neuron elements without interruption. The physiological conception of the synapse is sound and has to be maintained. But the neurone theory in its classical form as it was conceived in the first years of the cellular theory is false and does not take into sufficient account the more modern conceptions and facts regarding the minute structure of the multicellular body and of its nervous arrangements. In its classical form it must therefore be abandoned, but in its physiological aspects it will remain the basis on which our conceptions of the physiology of the nervous system are built. Even in the sympathetic end-formation with its reticular structure a synaptic arrangement remains necessary, but as soon as we

recognize that this synaptic arrangement consists of living alterable substance, without intercellular membranous barriers in which it would be impossible to locate the extremely delicate physiological properties we ascribe to synapses, we have to acknowledge that the classical neurone theory has to be abandoned and replaced by a new formula. As Dr. Young wrote to me, the question of the synapses is really the core of the matter. This question has to be studied morphologically and physiologically, but in this study it is dangerous to begin with the classical neurone theory as its unshakable basis, for this would lead us farther and farther away from the ascertained facts and hamper us in every respect, both histologically and physiologically.

It is always dangerous to label a scientist as 'neuronist' or as 'antineuronist'. We have simply to try to understand rightly the complicated structure of the nervous system, its enormous plasticity, and on the other hand its conservativeness. We do not need to adhere to obsolete conceptions and formulae of the last century. We need to form new paths, to achieve new outlooks, to admit that the structure of the body is far more complicated than the older scientists thought it to be. But in this we must not be impeded and obstructed by obsolete formulae, however important they may have been for the advancement of science in the past, and however important they remain. We have to search for a new basis or more modern structure than the old classical neurone theory.

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